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REVIEW

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Retrotransposon life cycle and its impacts on cellular responses

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ABSTRACT

Approximately 45% of the human genome is comprised of transposable elements (TEs), also known as mobile genetic elements. However, their biological function remains largely unknown. Among them, retrotransposons are particularly abundant, and some of the copies are still capable of mobilization within the genome through RNA intermediates. This review focuses on the life cycle of human retrotransposons and summarizes their regulatory mechanisms and impacts on cellular processes. Retrotransposons are generally epigenetically silenced in somatic cells, but are transcriptionally reactivated under certain conditions, such as tumorigenesis, development, stress, and ageing, potentially leading to genetic instability. We explored the dual nature of retrotransposons as genomic parasites and regulatory elements, focusing on their roles in genetic diversity and innate immunity. Furthermore, we discuss how host factors regulate retrotransposon RNA and cDNA intermediates through their binding, modification, and degradation. The interplay between retrotransposons and the host machinery provides insight into the complex regulation of retrotransposons and the potential for retrotransposon dysregulation to cause aberrant responses leading to inflammation and autoimmune diseases.

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Introduction

In addition to genic regions, our genome contains sequences that regulate gene expression, including those essential for the development, differentiation, and maintenance of cell/tissue homoeostasis, and those whose biological significance has not yet been clarified, such as mobile genetic or transposable elements (TEs). Although less than 2% of the genome is protein-coding, TE sequences comprise approximately 45% of the genome. The TE copy numbers have been amplified by their ability to mobilize throughout evolution. In addition, large-scale genomic alterations, such as segmental duplication, translocation, and chromosomal duplication, may have also contributed to the copy number changes. However, given the multifaceted role of TEs and the various associated phenotypes, defining their biological significance remains challenging.

The vast majority of TE sequences have lost their ability to 'jump' due to mutations; however, several lineages of these families are still capable of mobilization, resulting in insertional mutations. In addition, TE insertions are occasionally associated with more complex genetic instabilities, such as chromosomal deletions, duplications, and inter- or intra-chromosomal translocations [1–5]. To date, more than 100 TE insertion events have been suggested to be involved in disease-causing mutations [6]. TEs are classified into two major groups based on their mobilization mechanisms: DNA transposons and retrotransposons. DNA transposon sequences are excised from their original location and inserted into other genomic loci using a 'cut-and-paste' mechanism. In contrast, retrotransposons are transcribed by RNA polymerases and are converted into cDNA by reverse transcription in the nucleus or cytoplasm, depending on the class (Figures 1 and 2). This 'copy-and-paste' mechanism, termed retrotransposition, may have allowed these elements to be more efficiently amplified in the genome as retrotransposon sequences occupy nearly half of the human genome, whereas DNA transposons constitute only a small percentage [7].

De novo TE insertion is inherited when it occurs in the germline but can also occur in various somatic cells, resulting in genetic mosaicism in each individual. Generally, somatic TE expression is epigenetically silenced. However, the transcriptional repression of TE sequences has been suggested to be unleashed more often than expected. In many cancer cells, epigenetic modifications are aberrantly regulated, rendering these mobile elements transcriptionally active. Once expressed, those RNAs undergo translation to produce the components required for retrotransposition, including reverse transcriptases (RTs) that synthesize complementary DNA (cDNA). Retrotransposon-derived proteins form complexes with their encoding RNA, which may gain access to the nucleus where their cDNA copies are inserted. Intriguingly, as some of their families are non-coding sequences, these elements 'hijack' RTs from the other families to jump into the genome. TEs may have been domesticated or co-evolved

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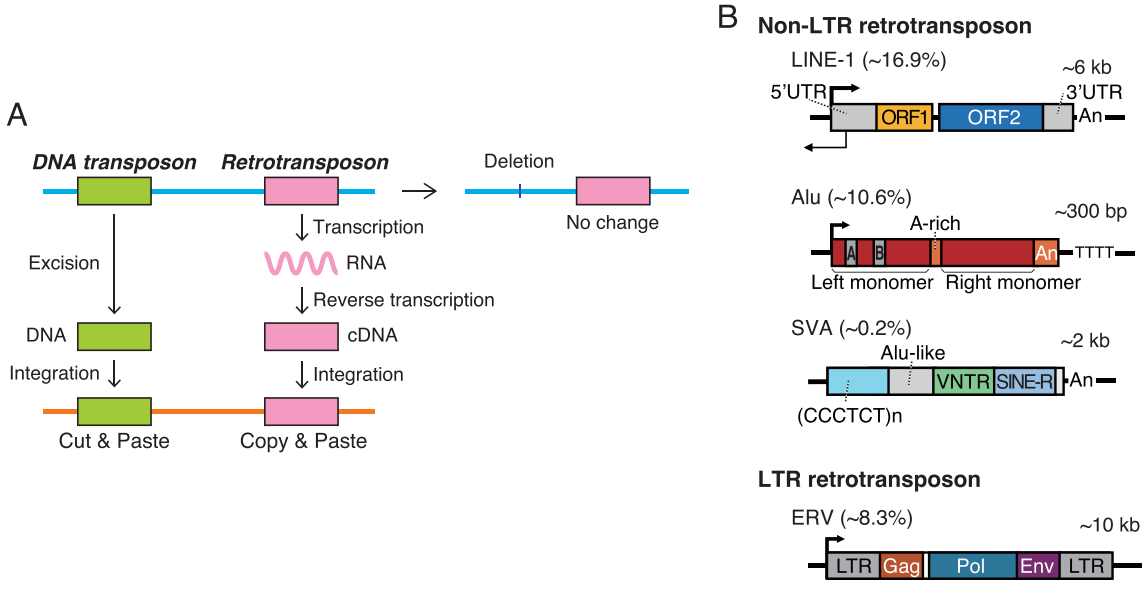

Figure 1. Classification of human retrotransposons. (A) Two distinct modes of transposition mechanisms. In a process known as 'cut and paste', a DNA transposon sequence (green box) is excised from the original genomic location (blue line) and then inserted into a new genomic location (orange line). Retrotransposons employ a 'copy and paste' mechanism for mobilization. In this case, the sequence (pink box) is transcribed into RNA, undergoes reverse transcription, and is subsequently integrated into another genomic location. (B) Structures and characteristics of human retrotransposons. Non-long terminal repeat (LTR) retrotransposons include long interspersed elements (LINE-1s or L1s) and short interspersed elements (SINEs), such as Alu and SVA. L1s comprise ~ 16.9% of the human genome. The full-length L1 is ~ 6 kb and includes a bi-directional promoter in the 5' untranslated region (UTR; left grey box), two open reading frames (ORF1 and ORF2; orange and blue boxes, respectively), and a 3' UTR (right grey box) with a poly(A) sequence. L1 ORF1 encodes an RNA-binding protein, while the protein encoded by L1 ORF2 possesses endonuclease (EN) and reverse transcriptase (RT) domains. Alu is the most abundant SINE and makes up ~ 10.6% of the genome. Alu is ~ 300 bp in length and characterized by the dimeric structure consisting of the left and right monomers (red boxes), which are separated by an adenosine-rich (A-rich) sequence (orange box). The left monomer contains conserved A and B boxes (grey boxes A and B) required for transcription. The right monomer ends with the terminal poly(A) sequence (orange box, An), followed by the flanking genomic DNA containing the RNA polymerase III termination signal (TTTT). SVA elements are typically ~ 2 kb in length and comprise ~ 0.2% of the genome. The structure of SVA contains hexameric CCCTCT repeats (light blue box), an inverted Alu-like repeat (grey box), a variable nucleotide tandem repeat (VNTR, green box), a SINE-R sequence derived from human endogenous retrovirus (HERV)-K (blue box), and a terminal poly(A) sequence (An). An LTR-type retrotransposon ERV is ~ 10 kb in length and present at ~ 8.3% in the genome. The full-length ERV sequence comprises 5' and 3' LTRs, identical sequences flanking the internal coding regions including the *gag*, *pol*, and *env* genes. These genes encode the viral capsid, catalytic components (reverse transcriptase, integrase, and protease), and envelope proteins, respectively.

within the host genome; therefore, they may have a functional interplay with host factors. Indeed, proteomic approaches and genetic screening have identified numerous proteins that regulate retrotransposon activity (*e.g.*, transcription, translation, and genomic insertion) (reviewed in [3,8]). More recently, in the retrotransposon amplification cycle, RNA and cDNA intermediates, or the processes that generate them, have been suggested to activate various host responses involved in innate immune and DNA damage responses. In particular, retrotransposon-mediated innate immune responses are implicated in several autoimmune disorders that involve complex interactions between interferon-stimulated gene products that typically inhibit retrotransposition and the associated innate immune responses. In this review, we provide an overview of the life cycle of human retrotransposons and their ongoing impacts on cellular responses. We also discuss how imbalances or deregulation of the host system lead to aberrant responses or disease-associated phenotypes linked to retrotransposons.

Overview of retrotransposons

While retrotransposons mobilize through RNA intermediates, DNA transposons transpose by moving discrete DNA sequences into the genome, rendering them inefficient for amplification (Figure 1A). Except for bats, the majority of DNA transposons in mammals are no longer active and are not capable of mobilization, whereas retrotransposons successfully expand and some manage to remain active [9,10]. Approximately 42% of the human genome is made up of retrotransposons, which are categorized into two groups: long terminal repeat (LTR) and non-LTR retrotransposons depending on the presence or absence of flanking LTRs in the 5' and 3' untranslated regions (UTRs).

Non-LTR retrotransposons

Non-LTR retrotransposons lack LTRs and retrotranspose via different mechanisms. Non-LTR retrotransposon family includes several types of elements, including long interspersed element-1 (LINE-1 or L1), short interspersed elements (SINE), and SINE-variable number of tandem repeat (VNTR)-*Alu* (SVA) elements (Figure 1B). Although the majority of the copies are truncated and mutated, the full-length L1 is ~ 6 kb in length and encodes a reverse transcriptase. The most prevalent SINE, Alu, is ~ 300 bp in length and is specific to primates. There are approximately one million copies of Alu in the human genome, which is double that of L1 copies at approximately 500 thousand. However, L1 sequences cover the most significant portion of the human

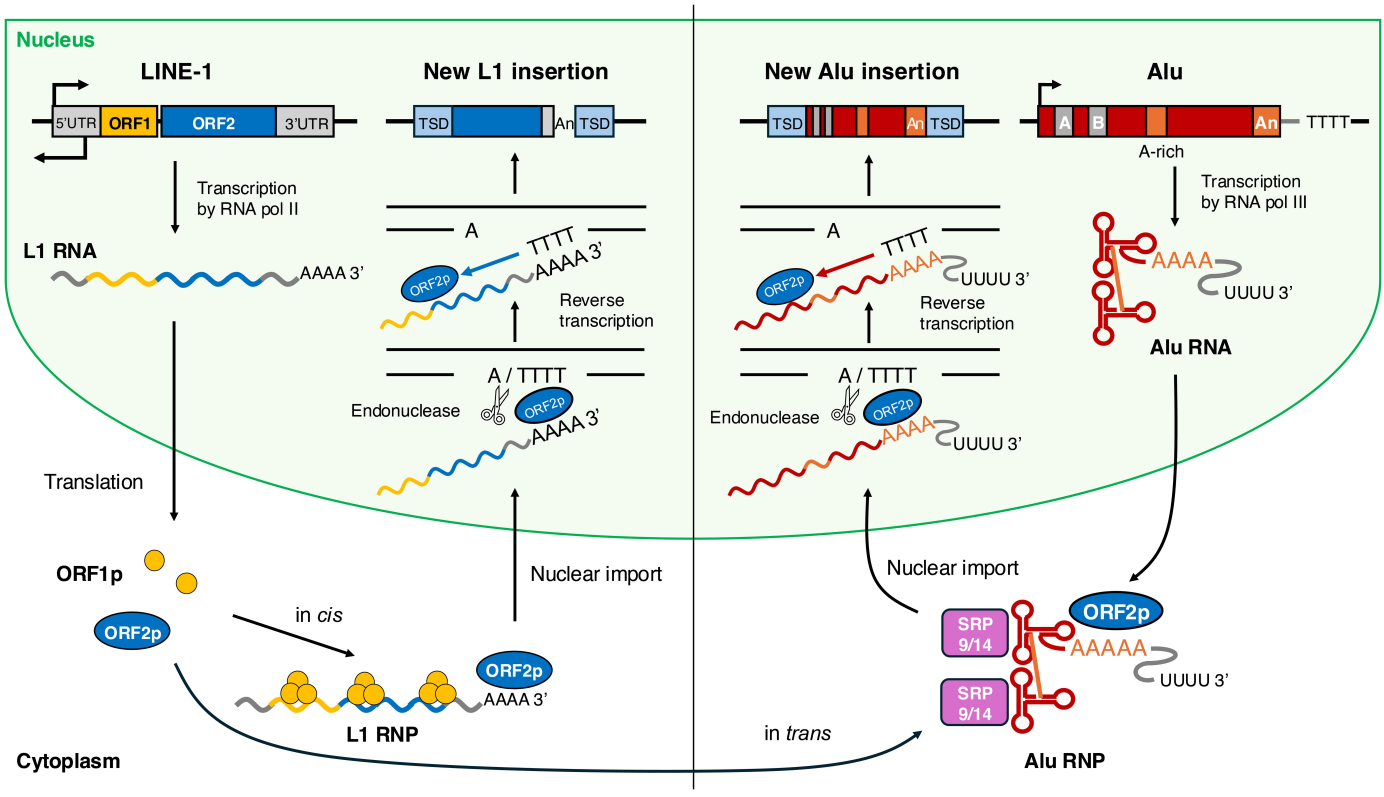

Figure 2. Model for L1 and Alu retrotransposition. RNA polymerase II drives L1 expression in the 5' UTR. L1 ORF1p (yellow circle) and ORF2p (blue ellipse) are translated into the cytoplasm and subsequently bind to their encoding L1 RNA in *cis* to form ribonucleoprotein particles (RNPs). In contrast to L1, Alu is transcribed by RNA polymerase III, which terminates at a T-rich sequence in the flanking genomic DNA. Alu RNA binds to the SRP9/14 heterodimer and L1 ORF2p binds in *trans* to form Alu RNP. Both L1 ORF1p and ORF2p are vital for L1 retrotransposition. In contrast, Alu retrotransposition requires L1 ORF2p, but not ORF1p. After L1 or Alu RNP enters into the nucleus with unknown mechanisms, L1 ORF2p endonuclease activity creates a nick in the genome at the degenerative consensus sequence (*e.g.*, 5'-TTTT/AA-3' the slash indicates the cleavage site). The L1 ORF2p synthesizes L1 or Alu cDNA using the resulting genomic DNA end as a primer. This process is termed target site-primed reverse transcription (TPRT). Consequently, double-stranded L1 or Alu cDNA is inserted into the genome; however, the detailed mechanisms underlying this process remain to be elucidated. The inserted L1 or Alu sequences have target-site duplications (TSDs) at both ends. While L1 retrotransposition frequently accompanies 5' truncation, full-length Alu insertion occurs with a high frequency.

genome (~17%), exceeding the coverage of Alu sequences (~11%), due to the size difference between the full-length L1 and Alu. The evolutionally young retrotransposon family, SVA, is typically ~ 2 kb in length and specific to hominids, comprising ~ 0.2% of the human genomic DNA. Although these retrotransposons actively retrotranspose in the genome, only L1 is autonomous; Alu and SVA do not code for proteins, but exploit L1-encoded reverse transcriptase for retrotransposition [11].

LTR retrotransposons

LTR retrotransposons, also known as endogenous retroviruses (ERVs), are retrovirus-like sequences integrated into the genome. ERV proviruses are made up of the flanking 5' and 3' LTRs, *gag*-, *pol*-, and *env*-expressing sequences (Figure 1B), possibly allowing expansion through reinfection in human ancestors [12]. However, the *env* sequences in LTR retrotransposons are commonly mutated, impairing cell-to-cell transfer, although some *env* sequences may remain functional [13]. Human endogenous retroviruses (HERVs) are categorized into three classes, I, II, and III, according to their sequence similarity to gammaretroviruses, betaretroviruses, and human spumaviruses, respectively. HERV is further subdivided based on the primer binding site (PBS) similarities with the tRNA sequence used to prime the HERV amplification process: for example, 3' end of the tRNA for lysine (K) matches the PBS of HERV-K, and tryptophan (W) for HERV-W [14]. To date, there have been no reports of HERV actively retrotransposing into the human genome, and HERV retrotransposition is thought to be defective.

Retrotransposon life cycle and its regulation

Epigenetic silencing

In somatic cells, retrotransposons are generally suppressed by DNA methylation and histone modifications for epigenetic silencing. The spread of retrotransposons in the genome shapes a complex gene regulatory network by providing binding sites for epigenetic suppressors and transcription factors. DNA methylation, H3K9, and H3K27 methylation are associated with chromatin suppression. These silencing marks are regulated by silencing complexes that recruit various histone methyltransferases and deacetylases. This includes tripartite motif-containing 28 (TRIM28), also known as KRAB-associated protein 1 (KAP1) [15] mediator, which is usually recruited by Kruppel-associated box zinc-finger proteins

(KRAB-ZFPs) that bind to retrotransposon sequences [16]. Besides KAP1, the human silencing hub (HUSH) complex [17,18] and the nucleosome remodelling and deacetylase (NuRD) complex [19] may also suppress retrotransposons expression. Removal of the chromatin modifiers globally upregulates retrotransposons, which typically occurs in dysregulated cells, such as cancer cells. Both L1 and ERV are transcriptionally repressed by suppressive epigenetic modifications such as histone H3K9 methylation mediated by several overlapping factors shown here [15,20–24]. DNA methyltransferases DNMT1 and DNMT3A/3B also participate in transcriptional repression by methylating the CpG sequences in the promoter regions of L1 and ERV [20,25–27]. As such, histone modification and DNA methylation may function in concert to silence L1 and ERV, although the mechanism governing Alu silencing seems to be different from these cases. While both DNA and histone methylation occur on Alu sequences, DNA methylation, which was previously thought to repress Alu transcription [28–30] may be required to inhibit recombination between Alu sequences; instead, histone methylation may play a vital role in the transcriptional silencing of Alu [31].

Upregulation of retrotransposons is one of the hallmarks of tumour progression, where a surge in TE expression reflects a compromised silencing system, as described in the previous paragraph [32]. The increase in retrotransposon expression may be caused by the loss of epigenetic silencing or mutations in retrotransposon inhibitors. p53, a central regulator of the cell cycle, whose loss can lead to cancer, also inhibits retrotransposon expression [33,34]. The first cancer driver mutation caused by retrotransposition was identified in the tumour suppressor *APC* gene, in which the last exon of *APC* was disrupted by the insertion of an L1 sequence, leading to colon cancer [35]. Notably, *BRCA1*, whose mutations predispose to breast and cervical cancer, inhibits L1 retrotransposition [36], whereas *de novo* retrotransposon insertions often occur in the *BRCA1/2* loci. Retrotransposition has also been implicated in a plethora of diseases [6].

Programmed transcription

Although the expression of retrotransposons in somatic cells is thought to be aberrant because most retrotransposons are epigenetically repressed, some retrotransposons expressions are programmed. The coordinated expression of TEs is vital during different developmental stages to increase chromatin accessibility and is indispensable during embryogenesis [37–40]. For example, MERVL, which is a mouse ERV that plays an indispensable role in maintaining the 2C cell stage during mouse embryonic development, has been suggested to modulate the chromatin state instead of the retrotransposon intermediates [41,42]. Taken together, these findings suggest that retrotransposons act as molecular switches during different stages of cell development.

Transcriptional change in response to stress and ageing

In addition to modulating chromatin, retrotransposons are expressed in response to cellular state changes such as heat stress and immune responses [43,44]. A reanalysis of public gene expression datasets that include gene expression post-infection by different viruses (including SARS-CoV-2, Ebola, measles, Rift Valley fever, influenza A, herpes simplex, and Zika viruses) showed that retrotransposons are upregulated after infection [44]. An emerging hypothesis suggests that the host may actively upregulate retrotransposon expression as a defence mechanism against pathogens by promoting the innate immune response due to some retrotransposon intermediates being immunogenic, as described later. However, the mechanism behind the retrotransposons upregulation is unclear [45]. Depletion of the suppressor of variegation 3–9 homolog 1 (SUV39H1), a methyltransferase that deposits H3K9 trimethylation (H3K9me3) at retrotransposon loci for epigenetic silencing, has been proposed as one of the mechanisms by which the host promotes retrotransposon expression during viral infection [46].

Epigenetic silencing declines throughout the human lifespan, leading to an increase in retrotransposon expression in older individuals. Simultaneously, the increased expression of retrotransposons may further accelerate ageing potentially through several mechanisms, including DNA damage during retrotransposition, increased retrotransposition activity that may disrupt genome stability, and innate immune activation by immunogenic retrotransposon intermediates that can cause inflammaging [47,48], as discussed in 'Retrotransposon-associated immune responses' section.

Transcription & translation

L1 transcription is driven by an internal RNA polymerase II promoter in the 910 bp L1 5' UTR. The promoter region in the 5' UTR recruits several transcription factors, such as Yin Yang 1 (YY-1), runt-related transcription factor 3 (RUNX3), and specificity protein 1 (Sp1) that bind to the L1 5' UTR [49–53]. Athanikar et al. showed that the YY-1 binding site is critical for full-length L1 transcription [54]. L1 5' UTR also harbours antisense promoter activity that transcribes in the opposite strand direction from 300–500 bp downstream from the beginning of the 5' UTR, resulting in chimeric RNA transcription, which includes the flanking sequence and 5' UTR [55,56]. The chimeric RNAs have the Kozak sequence and an AUG start codon, and are modified by splicing, polyadenylation, and capped structures. Thus, the antisense transcripts are translated into proteins known as ORF0 [57]. The function and biological significance of ORF0p remain unknown; however, overexpression of ORF0p increases L1 retrotransposition frequency, suggesting that ORF0 may facilitate L1 retrotransposition. L1 antisense promoter activity enhances the growth of cultured cells and may contribute to abnormal cell proliferation, such as in cancer; however, its effect on cell proliferation warrants further elucidation [58].

In retrotransposition-competent L1 sequences, two proteins are encoded: ORF1 protein (ORF1p) and ORF2 protein (ORF2p) [59–61] (Figures 1 and 2). Translation of L1 ORF1p is thought to be initiated in a cap-dependent manner [62]. However, L1 RNA is subjected to METTL3-mediated *N6*-methyladenosine (m^6A) RNA modification, which may recruit eukaryotic translation initiation factor 3 (eIF3) and

augment translation efficiency through a cap-independent mechanism [63]. Moreover, the mechanism of the bicistronic translation of L1 RNA is not fully understood. The translation of L1 ORF2p, which is encoded downstream of the *ORF1*-coding sequence with a stop codon, occurs in an AUG-independent manner, perhaps because of the reinitiation of ribosome scanning [64]. Many vertebrates, including mice, possess a putative internal ribosomal entry site (IRES) between the *ORF1* and *ORF2*-coding sequences to initiate L1 ORF2p translation; however, no IRES activity has been reported in human L1s [65,66].

L1 ORF1p is an RNA-binding protein with nucleic acid chaperone activities [67–69], whereas L1 ORF2p is an RT that possesses endonuclease (EN) activity [61,70,71], both of which are essential for L1 retrotransposition. In the cytoplasm, these two proteins preferentially bind to L1 RNA in *cis* to form ribonucleoprotein particles (RNPs) [67,72] (Figure 2). L1 ORF1p is critical for L1 RNP formation, whereas the ORF2p EN and RT activities are not [73]. L1 RNP formation is also a prerequisite, but insufficient for L1 retrotransposition [72].

Alu sequences may have evolved from 7SL RNA, which is a component of signal recognition particles (SRPs) [74]. A full-length Alu sequence is formed by the two Alu domains (left and right monomers) derived from the 7SL RNA (Figure 1B). These domains are separated by an adenine-rich sequence, and the remaining domain contains an internal promoter, A and B box sequences that are required for Alu transcription by RNA polymerase III [75]. Alu RNA preserves binding sites for the SRP component, the SRP9/14 heterodimer, which facilitates Alu retrotransposition [76,77]. In general, RNA polymerase III-mediated Alu transcription is repressed [30]; however, its expression levels increase in response to various stress conditions, including viral infection, heat stress, DNA damage, and translation inhibition [43,78–81]. Notably, Alu expression plays a multifaceted role in stress response. For instance, heat stress-induced Alu RNA interacts with RNA polymerase II and inhibits its binding to the target promoters, thereby regulating gene expression that is not essential for this response [82,83]. Intriguingly, Alu RNA undergoes degradation during heat stress owing to its self-cleavage activity, which, in turn, negates its inhibitory effect on RNA polymerase II [84,85], suggesting negative feedback regulation. Furthermore, while SRP9/14 associates with 40S ribosomal subunits to promote the accumulation of stress granules, which are cytoplasmic membrane-less organelles formed in response to various types of stress to temporarily store and triage untranslated mRNAs, Alu RNAs may also contribute to stress granule instability by sequestering SRP9/14 from the 40S ribosome upon recovery from stress [78].

Some LTRs are transcribed by RNA polymerase II, either through the internal promoter in the LTR region or another upstream promoter. Therefore, even with a single LTR, known as a solo LTR retrotransposon, LTRs can drive the expression of downstream genes [86]. Indeed, some LTR retrotransposons serve as gene expression regulators, as evidenced by ERV1, which provides binding sites for octamer-binding transcription factor 4 (OCT4) and the homeobox transcription factor NANOG during embryogenesis. ERV1 provides distinct regulatory networks in humans and mice [87], suggesting species-specific regulation by ERVs. Another well-studied ERV that functions as a gene expression regulator in humans is LTR7 or HERV-H, which has been proposed to act as an enhancer, long non-coding RNA, and promoter [88]. Although most HERVs have lost their protein-coding potential owing to mutations throughout evolution, some HERVs have intact ORFs that code for proteins beneficial for the host. For example, Suppressyn is an *env*-derived receptor-binding protein that inhibits mammalian type D retroviruses through competitive receptor binding [89]. However, some HERV sequences, such as HERV-K, may be detrimental and contribute to neurodegenerative diseases [90]. These examples demonstrate the dual impact of HERV expression on the host.

Some ERV proteins are repurposed for host cellular functions; a classic example is the domestication of an ERVW-1 *env* sequence, known as *syncytin-1* gene. This gene is repurposed for cell-cell fusion during placental formation [91]. In 2018, two studies described an unexpected function of a gene derived from the *gag* sequence of ERV known as Arc. Despite having only the *gag* protein, Arc was shown to assemble into a capsid akin to non-enveloped viruses and mediate intercellular mRNA transfer between neurons in rats [92] and fruit flies [93]; a similar function has been suggested in humans, as mutations in Arc are associated with neurological disorders [94]. Additional domesticated HERV-derived proteins are expected to be identified in future.

Genomic integration

Although LTR retrotransposons no longer retrotranspose in humans, non-LTR retrotransposons, including L1, Alu, and SVA, remain active in the human genome. L1 is the only autonomous retrotransposon in the human genome; however, Alu and SVA, which do not have protein-coding sequences, rely on L1 ORF2p activities for retrotransposition. Figure 2 shows a schematic of the L1 and Alu amplification cycles. In L1, both L1 ORF1p and ORF2p bind to the L1 RNA in *cis* to form the L1 RNP complex. It has been suggested that L1 RNPs accumulate and form phase-separated bodies unique to L1 [73,95–97]. These L1 bodies interact with stress granules and P bodies, as well as with the proteins inside. However, the necessity of L1 body formation for L1 nuclear transport and retrotransposition remains unclear. Meanwhile, a plethora of innate immune factors have been identified and are colocalized in stress granules, P bodies, and/or L1 bodies, some of which are known to substantially inhibit L1 retrotransposition. L1 RNPs are targeted by several host defence mechanisms, as described in a later section.

The mechanism by which L1 RNPs are imported into the nucleus remains unclear. However, it seems that nuclear membrane breakdown is not the only pathway, because L1 in non-dividing cells can also retrotranspose [98]. L1, Alu, and SVA are integrated into the human genome through a mechanism called target site-primed reverse transcription (TPRT) [99,100]. Once L1 RNPs enter the nucleus, the L1 ORF2p EN creates a single-stranded (ss) DNA nick at the degenerative site of TTTT/AA (slash indicates the L1 ORF2p cleavage site) [70,99,101], which may be associated with DNA double-strand break (DSB) formation [102–104]. The T-rich

sequence cleaved by the L1 ORF2p EN activity complementarily binds to the L1 RNA poly(A) tail [105,106]. Subsequently, L1 ORF2p reverse transcribes the first strand of L1 cDNA from L1 RNA using cleaved genomic DNA as a primer. Despite studies on L1 retrotransposition mechanisms, the second-strand genomic DNA cleavage, second-strand L1 cDNA synthesis, and L1 cDNA ligation to genomic DNA remain unclear [3,11]. However, several studies on the host factors that facilitate L1 retrotransposition have hinted at these questions. For instance, a cellular RNase H may degrade L1 RNA during or after reverse transcription to synthesize second-strand L1 cDNA [107]. Moreover, poly (ADP-ribose) polymerase 2 (PARP2) recognizes ssDNA breaks induced by the L1 ORF2p EN activity and subsequently recruits replication protein A (RPA), which may protect ss L1 cDNA from C-to-U editing by apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3A (APOBEC3A) cytidine deamination, which significantly inhibits L1 retrotransposition [104,108]. L1 ORF2p may directly interact with proliferating cell nuclear antigen (PCNA), a sliding clamp for DNA polymerases, via the PCNA-interacting protein (PIP) box within L1 ORF2p [109], suggesting an increase in the processivity of L1 ORF2p-mediated reverse transcription. While second-strand cleavage may occur downstream of the first-strand nick sites, DNA templates of Okazaki fragments during S phase are also preferentially targeted by the L1 ORF2p EN activity, supporting the idea that such a pre-existing DNA gap or nick can be employed for L1 cDNA insertion [101,110,111]. Consequently, second-strand DNA cleavage or unligated Okazaki fragments may result in the generation of target site duplications (TSDs) at both ends of the inserted L1 cDNA, which is a hallmark of L1 retrotransposition [1,2,5,61]. If this second-strand cleavage or a DNA gap occurs upstream of the first cleavage site by L1 ORF2p, L1 retrotransposition results in a target-site deletion.

While L1 ORF1p and ORF2p are indispensable for L1 retrotransposition, Alu does not strictly require L1 ORF1p for its retrotransposition; however, instead, Alu RNAs can 'hijack' L1 ORF2p from L1 RNPs. SRP9/14 binds to Alu RNA, forming Alu RNP, which exhibits preferential association with stalled ribosomes, efficiently recruiting L1 ORF2p being translated from L1 RNA to the poly(A) tract on Alu RNA [76]. This poly(A) tract on Alu RNA mimics the poly(A) tail in the L1 3' UTR, which is necessary for L1 ORF2p binding to L1 RNA [105,111,112]. Intriguingly, two distinct types of HeLa cell lines have recently been characterized, one of which is capable of supporting Alu retrotransposition, whereas the other is not; however, L1 retrotransposition efficiently occurs in both cell types [113]. The detailed mechanisms underlying differences in the regulation of L1 and Alu retrotransposition remain unclear. In the case of SVA, L1 ORF1p is not essential, but augments SVA mobilization [114,115]. Both Alu and SVA retrotranspositions are also accompanied by the typical features observed in those of L1 retrotransposition, such as degenerative L1 ORF2p cleavage sites, TSD formation, and poly(A) sequences at the 3' region [116]. Taken together, previous studies suggest that while non-LTR retrotransposons share L1 ORF2p in retrotransposition, each one of them employs a different mechanism.

Regarding LTR retrotransposons, despite HERV retrotransposition being defective, HERV can reverse transcribe RNA into cDNA as long as the proteins remain functional; some HERV-K RTs have been found to be active [117]. HIV-1 RT is a suitable reference for HERV-K RT studies as HIV-1 is a well-studied retrovirus. A comparison of RT inhibitors revealed that nucleoside inhibitors, such as zidovudine inhibit both HIV-1 and HERV-K RT, whereas non-nucleoside inhibitors such as nevirapine and efavirenz only inhibit HIV-1 RT, suggesting structural differences between the two RTs. Unlike HIV-1 RT, HERV-K RT forms a heterodimer. Although the RT mechanism of HERV-K is similar to that of HIV-1 RT, especially in the active sites, structural analyses suggest that HERV-K RT shares a higher similarity with the yeast retrotransposon, Ty3 RT, with some unique structural features [118]. Unlike non-nucleoside RT inhibitors, nucleoside RT inhibitors represent a promising avenue for general RT inhibition because they can also inhibit L1 ORF2p RT [119].

RNA modification and structure

Eukaryotic mRNA is subjected to several post-transcriptional modifications, with the m^{6}A RNA modification being the most abundant [120]. Approximately 22% of the nascent RNAs undergoing m^{6}A modification are enriched in L1 sequences, indicating that L1 RNAs are highly susceptible to m^{6}A modification in humans [121]. The human and mouse L1 RNAs are methylated by the m^{6}A 'writer' proteins methyltransferase-like 3 (METTL3) and METTL14, and demethylated by the 'eraser' proteins AlkB homolog 5 (ALKBH5) and fat mass and obesity-associated (FTO) protein [121,122]. m^{6}A modification regulates the expression of L1 and L1 containing genes. In the human-specific L1 subfamily L1-Hs, m^{6}A modification by METTL3 increases the translation efficiency of L1 RNA and facilitates L1 retrotransposition [63] (Figure 3). This m^{6}A modification cluster, located on the L1 5' UTR within an RRACH consensus motif (R = G/A, and H = U/C/A), serves as a docking site for eIF3, enhancing translational efficiency and promoting L1 RNP formation. Furthermore, comparative analysis of L1 RNA sequences in humans, chimpanzees, and gorillas revealed that m^{6}A motifs occur more frequently in younger L1 subfamilies, suggesting that m^{6}A is a driving force in L1 evolution [63]. Similarly, in mice, METTL3/14 knockout reduces younger L1 RNA levels, suggesting that m^{6}A modification may facilitate evolutionarily younger L1s [123]. Conversely, the m^{6}A 'reader' protein YTH domain-containing protein 1 (YTHDC1), which recognizes m^{6}A-modified L1 RNA and recruits host factors, inhibits L1 through both transcriptional repression and RNA degradation. During mouse embryogenesis, YTHDC1 suppresses L1 transcription by recruiting TRIM28 (also known as KAP1), the HUSH complex, and SET domain-bifurcated histone lysine N-methyltransferase 1 (SETDB1) [124,125]. Moreover, the HUSH complex collaborates with the nuclear exosome-targeting (NEXT) complex to degrade L1 RNA in mouse embryonic stem [122,125]. This L1 m^{6}A-mediated regulation plays an important role in mouse embryonic development [120,124]. Recent studies have demonstrated that scaffold attachment factor B (SAFB), which binds to L1 RNA via m^{6}A modification, inhibits L1

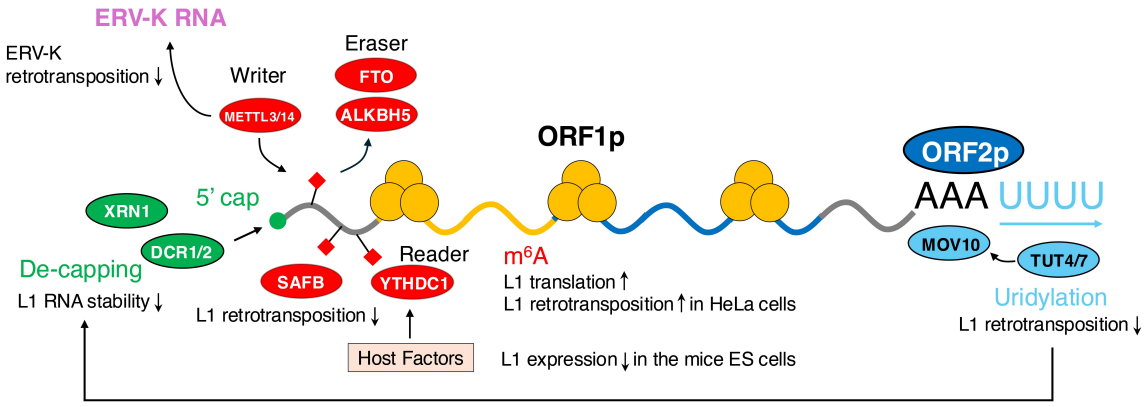

Figure 3. RNA modifications on L1 RNA. Several proteins are involved in modifying and regulating L1 RNA metabolism. L1 RNA is modified with *N6*-methyladenosine (m^6A) (red rectangle) by the 'writer' proteins METTL3/14, which can be reversed by the 'eraser' proteins ALKBH5 and FTO. In mouse embryonic stem cells, L1 RNA with m^6A is recognized by the 'reader' protein YTHDC1, leading to transcriptional repression in collaboration with host factors. In contrast, this modification augments L1 protein translation in HeLa cells by recruiting eIF3. SAFB also binds to L1 RNA via m^6A modification and inhibits L1 retrotransposition. Additionally, MOV10 recruits terminal uridylyltransferases TUT4/7 and facilitates uridylation (light blue) at the 3' end of L1 RNA, thereby inhibiting L1 retrotransposition through multiple mechanisms. L1 translation primarily occurs in a cap-dependent manner, with a 7-methylguanylate cap at the 5' end (green circle); however, uridylated L1 RNA can also be targeted by decapping enzymes such as DCP1/2, potentially leading to subsequent degradation by XRN1 exonuclease. Although it has been suggested that m^6A modification also occurs on ERV-K RNA, which is regulated by the METTL3/14, and that 5'-triphosphate modification is present in Alu RNA, the detailed mechanisms underlying these regulations remain to be elucidated.

retrotransposition [121,126]. Moreover, SAFB also regulates RNA splicing, ensuring that L1 sequences embedded in mRNA introns remain unexonized, thereby preventing their inclusion in mature mRNA transcripts. In contrast, under heat stress conditions, L1 sequences can become exonized, leading to changes in the expression of the L1-containing genes. This suggests that L1s contribute to gene expression diversity not only through insertional mutations via retrotransposition, but also by influencing exonization in response to environmental conditions [121,126]. Based on these findings, m^6A can act as both a facilitator and suppressor of L1 expression and retrotransposition, perhaps depending on the cellular state (during embryogenesis and post-differentiation, etc.) and species (human and mouse, etc.). Further analysis of the post-transcriptional modifications of L1 may address this contradiction.

Notably, as compared to L1, the opposite impact of m^6A RNA modification is observed on ERV RNAs. In mice, genome-wide CRISPR-based loss-of-function screening has revealed that m^6A writer METTL3/14 inhibits retrotransposition of ERV-K elements including intracisternal A-particles (IAPs), possibly by decreasing ERV-K RNA stability [123]. Similar to human L1 RNA, IAP RNA contains conserved RRACH sequence motifs that serve as m^6A modification sites. The abundance of IAP RRACH motifs in the 5' UTR directly correlates with the extent of m^6A modification [123]. In humans, HERV-H (also known as LTR7) is another retrotransposon that undergoes m^6A RNA modification. HERV-H regulates transcription of long non-coding RNA LINC-ROR, which subsequently influences human embryonic stem cell (hESC) differentiation [127]. The m^6A modification on HERV-H RNA is bound by YTHDC2, and this binding leads to recruitment of the DNA 5-methylcytosine(5mC)-demethylase TET1. This process results in DNA demethylation of HERV-H, which increases its expression. Notably, the depletion of YTHDC2 increases epigenetic silencing on HERV-H, suggesting that m^6A modification on HERV-H can regulate hESC fate [127].

The poly(A) sequence at or near the 3' end of L1 or Alu RNA is essential for L1 and Alu retrotransposition [105,112,128]. Warkocki and colleagues have demonstrated an inhibitory effect of uridylation at the 3' end of L1 RNA on L1 retrotransposition [129,130] (Figure 3). Moloney leukaemia virus 10 (MOV10), an RNA helicase, plays a crucial role in this process by interacting with L1 RNPs and recruiting terminal uridylyltransferases TUT4 and TUT7 (TUT4/7) [129,131]. These enzymes mediate the 3' terminal uridylation of mRNA and contribute to global mRNA decay [132]. The mechanism of L1 RNP regulation involves several steps. TUT4/7 uridylates L1 RNA. Subsequently, the uridylated L1 RNA is decapped by the decapping protein DCP1/2, followed by 5' to 3' exoribonuclease 1 (XRN1)-mediated degradation, suggesting L1 RNA is subjected to stepwise regulation, whereby uridylation, de-capping, and RNA degradation occur in a sequential manner [129,130]. Moreover, the presence of a poly-(U) sequence at the 3' end of uridylated L1 RNA prevents it from annealing with the ss T-rich genomic DNA end, thereby reducing efficiency of reverse transcription by L1 ORF2p.

In mammalian L1s, the 3' UTR is less conserved across species; however, its length is relatively longer and the GC content is higher than those in the other vertebrates [66]. L1 DNA and RNA contain potential quadruplex sequences (PQSs) in the G-rich region of its 3' UTR, which may facilitate L1 retrotransposition [133,134]. However, other reports have shown that the deletion or replacement of the G-rich sequence does not significantly alter L1 retrotransposition efficiency [61,104]. Evolutionary young subfamilies of human L1, SVA, and LTR retrotransposons tend to have more PQSs, whereas Alus have fewer [133,134]. Alu RNA forms a specific secondary structure, leading to the hypothesis that the formation of this Alu-specific RNA structure may be advantageous for retrotransposition [76]. However, it remains unclear whether

G4 structures within retrotransposon sequences function in DNA, RNA, or both and their precise functions require further elucidation.

Alu RNA, transcribed by RNA polymerase III lacks the 5' cap structure observed in canonical mRNA, including L1 RNA. Instead, it possesses a triphosphate group at its 5' end, a common feature of RNA polymerase III transcripts [135]. However, RNA with a triphosphate group at the 5' end can be recognized by RIG-I, a cytoplasmic sensor that detects viral RNA (more details in the next section) [136–138]; therefore, Alu RNA likely undergoes processing or is masked by RNA-binding proteins to prevent RIG-I recognition. The 5' phosphorylation state of Alu RNA appears to be regulated by DUSP11, which can process a triphosphate group at the 5' end to a monophosphate group [139]. Moreover, given that 7SL RNA is bound by SRP9/14, which shields the 5' end from RIG-I detection [140–142], it is likely that Alu RNAs may have retained this protective feature. The conserved secondary structure shared by Alu and 7SL RNAs [143] further supports this hypothesis. However, it should be emphasized that the exact mechanisms of potential Alu RNA protection require further investigation.

Intragenic Alu sequences are also transcribed by RNA polymerase II as part of the mRNA, potentially regulating gene expression through Alu exonization or alternative polyadenylation. SRP9/14 and nuclear DExH-box helicase 9 (DHX9) control splicing by suppressing Alu exonization and regulating secondary structures formed by intronic Alu sequences inserted in the sense direction of genes [144]. In contrast, hnRNPC binds to the poly(U) tracts of antisense Alu sequences, competing with the splicing factor U2AF65 (U2 small nuclear RNA auxiliary factor 65) to suppress aberrant splicing and Alu exonization [145]. When two or more Alu copies are placed in opposite directions on the same RNA molecule, this inverted-repeat Alu (IRAlu) can anneal to each other to form a double-stranded (ds) RNA. The IRAlu-directed dsRNA formation, often found in introns and 3' UTRs, impacts RNA editing, immune responses, circular RNA generation through backsplicing, subcellular localization, and STAU1-mediated mRNA decay (SMD), which regulates mRNA stability [146,147]. DHX9 resolves these secondary structures, reducing accumulation of immunogenic dsRNAs and circular RNAs [148]. Adenosine deaminase, acting on RNA 1 (ADAR1)-mediated A-to-I editing, preferentially targets these dsRNAs, facilitating the association of IRAlu-containing RNAs with nuclear paraspeckle components, including nuclear-enriched abundant transcript 1 (NEAT1), leading to their nuclear retention and translational inhibition [149]. This process can be modulated by alternative polyadenylation, where cleavage of the IRAlu sequence in the 3' UTR by cleavage stimulation factor subunit 2 (CSTF2) results in 3' UTR shortening [150]. Of note, nuclear retention of IRAlu-containing RNAs may not occur in hESCs because of low NEAT1 expression [151], suggesting the need for spatiotemporal regulation of Alu-containing gene expression during development.

Retrotransposon-associated immune responses

Pathogen infections usually carry signatures that are thought to belong to the pathogen that the host can identify to commence an immune response. Therefore, the term pathogen-associated molecular pattern (PAMP) was introduced. However, there are some common features between PAMPs and endogenous elements that trigger an immune response. Retrotransposons and other endogenous elements were recently discovered to trigger immune responses; therefore, the term 'immunogen' is used, instead of PAMP, in this review.

The innate immune system detects invading pathogens and acts as the first intracellular defence system that broadly detects different types of immunogens. A major component of innate immune response identifies pathogens through nucleic acid sensing, namely toll-like receptors (TLRs) and RIG-I-like receptors (RLRs) for RNA sensing, and absent in melanoma 2 (AIM2) and cyclic GMP-AMP synthase (cGAS) for DNA. Although intracellular nucleic acid sensing is vital for activating robust antiviral responses, the same system can also be triggered by self-nucleic acids. One example is Y RNA, a small non-coding RNA component of the Ro60 ribonucleoprotein particle, a common autoantibody found in patients with lupus autoimmunity [152]. It is unclear if this self-triggering of the innate immune response occurs due to imperfections in the sensors to differentiate between self and non-self, or if there is an evolutionary advantage in maintaining a basal level of innate immunity. The answer may apply to both as innate immunity evolves to combat invading pathogens and simultaneously repurpose the invaders for cellular processes or to prepare for future invasions. If innate immune system detection is imperfect, it can be expected that such broad-detecting immunity may be triggered by self-nucleic acids; however, the finding that some elements that have been co-evolving with the host for millions of years, such as retrotransposons, trigger innate immune responses supports the idea that there is an advantage of having a self-innate immune response trigger. Nevertheless, the discovery that retrotransposons can induce an innate immune response raises both questions and hopes in demystifying immune-related diseases. Focusing on retrotransposons, this phenomenon suggests two possibilities: an ongoing arms race between retrotransposons and the host; second, the self-activated immune response poses some evolutionary advantages, such as modulating the immune response level, or as a danger signal for aberrant transcription, as retrotransposons are usually epigenetically silenced in somatic cells [15,18,19,24,153].

Clear evidence of how retrotransposons induce innate immunity was provided by Stetson et al. study on three prime exonuclease 1 (TREX1) [154]. TREX1 is a 3' to 5' DNA exonuclease, in which mutations can cause the rare autoimmune disease Aicardi-Goutières syndrome (AGS) [155]. TREX1 was suggested to metabolize cDNAs derived from the L1 ORF2p RT, as TREX1 knockout resulted in the accumulation of retrotransposon DNA fragments in the cytoplasm, including L1s, SINEs, and LTRs. These cytoplasmic DNA fragments trigger the cGAS-STING pathway, strongly inducing an innate immune response. Stetson's model was further recapitulated by Thomas et al. [156], who showed that TREX1 reduces toxic L1 cDNA in neurons and astrocytes. In 2019, two studies showed L1-derived inflammation contributed to ageing in mice and RT inhibitors can ameliorate ageing phenotypes,

supposedly through inhibiting cDNA production by ORF2p RT [157,158].

Both retrotransposon cDNAs and RNAs have been reported to induce innate immunity. However, the mechanisms by which retrotransposon RNAs trigger innate immune responses remain unclear (Figure 4). In this section, we discuss how retrotransposons affect innate immunity, while emphasizing retrotransposon RNA immunogenicity and their regulation.

Mechanisms of immune response to retrotransposon RNA

Mutagenic insertion of a non-LTR retrotransposon SVA element in an important gene involved in transcriptional regulation, *TAF1*, causes intron retention, subsequently reducing TAF1 amount, which is linked to a neurodegenerative disease known as X-linked Dystonia Parkinsonism [159]. This insertion event provides important evidence that retrotransposition can drive neurodegenerative diseases. However, mutagenic insertion is rare, and retrotransposon-derived inflammation may be more common in diseases. More insights into the immunogenicity of retrotransposons and their impact on various diseases are expected to emerge as this topic gains the attention of researchers across different fields.

As discussed in the previous section, retrotransposon intermediates exist in different forms including ssRNA, RNA with secondary structures, RNA/DNA hybrids, and cDNAs produced by L1 ORF2p or HERV RT. The detection of cytoplasmic cDNA derived from retrotransposons can trigger an innate immune response through the cGAS-STING pathway in several disease models and during cellular senescence (irreversible arrest of cell division, a hallmark of ageing) [157,158,160–162]. Senescent cells commonly display senescence-associated secretory phenotypes (SASPs), characterized by increased secretion of inflammatory cytokines, chemokines, proteases, and

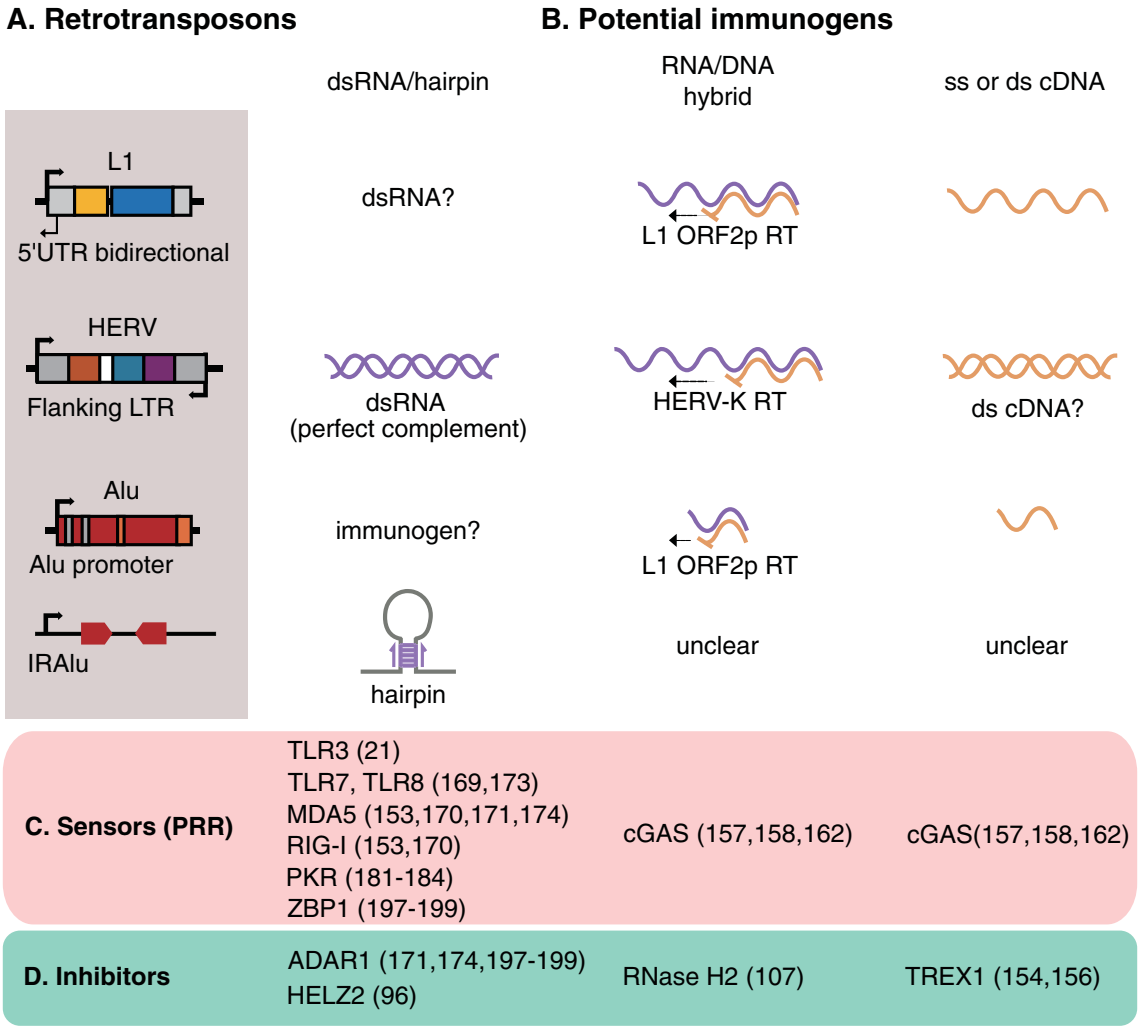

Figure 4. Potential immunogenic retrotransposon intermediates. (A) Retrotransposon families including L1, HERV, and Alu sequences are shown with the corresponding promoters. L1 contains a bidirectional promoter in the 5' UTR region, while HERV with solo LTR is expressed from one direction. In contrast, the full-length HERV has LTR promoters at both ends, which facilitate transcription of the full-length HERV from both directions. Full-length standalone Alu is expressed by RNA polymerase III, whereas two or more copies of Alus in the opposite orientation are expressed by an upstream promoter, which can form inverted repeat Alu (IRAlu). (B) Potential immunogens from either L1, HERV, or Alu corresponding to the left side retrotransposon sequence include dsRNA or hairpin formation, RNA/DNA hybrids, or reverse-transcribed cDNAs. (C) Recognition factors of retrotransposon intermediates are depicted. Pattern-recognition receptors (PRRs) may sense the retrotransposon intermediates to activate type I interferon. The relevant reference numbers are included for each PRR. (D) A number of inhibitors have been identified that destabilize these intermediates. The relevant reference numbers are included for each inhibitor.

growth factors [163,164]; retrotransposons activation may increase inflammatory cytokines production and exacerbate ageing-associated diseases. Inhibiting this immune response either through cGAS-STING knockdown or reverse transcription using RT inhibitors can ameliorate the observed inflammatory phenotypes [157,158]. Although HERV RT is capable of cytoplasmic reverse transcription [117,161], it was unclear whether L1 ORF2p RT can do the same as the reverse transcription was suggested to occur exclusively in the nucleus through the TPRT mechanism [70,99,100]. Hence, the cytoplasmic cDNA from L1 was thought to originate from aborted retrotransposition [165]. Recent findings, however, suggest that L1 ORF2p can reverse transcribe both Alu [162] and L1 RNAs [119] in the cytoplasm, possibly through self-priming using a 3' poly(U) tract for Alu, or using unknown RNA or DNA primers for L1, respectively. cGAS is mainly activated by dsDNA [166] or RNA/DNA hybrid [167]. While it is perhaps unlikely for L1 ORF2p to form ds cDNA in the cytoplasm, RNA/DNA hybrids are more likely to be substrates for L1 and Alu that activate cGAS. However, HERV can produce dsDNA in the cytoplasm because retroviruses can form dsDNA in the cytoplasm before nuclear import and genomic integration [168]. Unlike DNA, RNA is abundant in the cytoplasm, which makes the detection of non-self RNAs more difficult. Thus, RNA sensors have evolved to specifically detect specific RNA modifications and structures. Although much attention has been given to the immunogenicity of cDNA produced by L1 ORF2p, L1 [153,169,170], Alu [171–174], and ERV [21,23], RNAs can also trigger an innate immune response through the RLR and TLR pathways. However, the specific RNA structures of the immunogenic retrotransposons are not fully understood and require further investigation. In this section, we outline known retrotransposon intermediates that can trigger innate immune responses (Figure 4).

(I) *L1* - Although MDA5, RIG-I, TLR7, and TLR8 have been reported to detect L1 RNA to induce an innate immune response based on their respective downstream pathways [153,169,170], the exact mechanisms underlying these processes require further elucidation. It is still unclear whether L1 RNAs form long dsRNAs, hairpin structures, or RNA/DNA hybrids that can trigger the RNA sensors. One explanation for this is that L1 contains an antisense promoter that may produce antisense L1 RNA to form dsRNA. However, the antisense promoter is located in the L1 5' UTR, and only a short sequence of < 500 bases may complement sense-transcribed L1 RNA, making the L1 dsRNA rather short (MDA5 efficiently detects dsRNA of > 1000 bases) [175]. Tunbak et al. hypothesized that antisense L1 may be transcribed by a different antisense promoter, such as a lncRNA promoter, making it possible for full-length L1 to form a long dsRNA of ~ 6 kb [153]. On another note, full-length exogenous L1 RNA derived from a single copy has also been shown to trigger the innate immune response, suggesting that there may be a different mechanism for how L1 RNA triggers the response, or another unknown antisense promoter in the coding region and/or 3' UTR of L1 [96,170,176]. Although both exogenous and endogenous L1 RNAs may form dsRNAs, they are less likely to occur in cell lines with low endogenous L1 expression. A more likely explanation is that RNA/DNA hybrid formation, RNA secondary structure, or RNA modifications cause L1 RNA to be immunogenic. Owing to the potential immunogenicity of L1 intermediates, L1 ORF1p levels have been investigated in patients with autoimmune systemic lupus erythematosus (SLE). L1 ORF1p and L1 ORF1p autoantibodies were found to be relatively higher in SLE patients in comparison to the healthy controls, suggesting that L1 may have a role in systemic autoimmune diseases [177,178].

(II) *Alu* - Full-length Alus are only approximately 300 bases in length; however, dsRNAs with standalone Alus transcribed by RNA polymerase III have been suggested to form and induce an innate immune response despite their short length [179]. It is unclear which form of Alu RNA induces the immune response, as other transcripts containing Alu have been reported to induce innate immune responses through the formation of dsRNA by IRAlu in longer transcripts [171,180]. An MDA5 protection assay revealed that IRAlu is the most abundant retrotransposon bound to MDA5 [171], suggesting that dsAlu RNAs strongly trigger immune responses through the MDA5-MAVS pathway. However, as previously mentioned, ADAR1-mediated RNA editing of dsRNA containing IRAlu sequences mitigates recognition by MDA5, thereby substantially reducing the innate immune response [172,174,181]. In addition to RNA editing, RNA-binding proteins, such as Ro60, can also reduce immune responses, possibly by reducing or masking Alu RNA, thereby preventing its detection by ssRNA sensors, such as TLR7 [173]. However, it remains unclear whether Ro60 binds to immunogenic IRAlu-mediated dsRNAs. Another possibility, though less likely, is that Ro60 may bind to Alu RNA to prevent cDNA reverse transcription by L1 ORF2p. IRAlu is known as one of the endogenous dsRNAs that interact with protein kinase R (PKR) [182–184]. dsRNA-binding proteins, such as STAU1 and ADAR1, inhibit PKR activation by competing with PKR for binding to dsRNA [181,182]. However, there is an ongoing debate regarding whether ADAR1 RNA editing activity contributes to the inhibition of PKR activation [172,181]. Immunogenic Alu contributes to age-related macular degeneration (AMD), suggested to be through the cGAS-STING pathway (cDNA and/or RNA/DNA hybrid) [185].

(III) *HERV* - HERVs may modulate innate immunity through the regulation of innate immune loci expression. For instance, the loci of the primate major histocompatibility complex (MHC) have a high density of ERV [186]. Furthermore, HERV-derived LTR has also been shown to function as an enhancer that

regulates innate immunity [187]. Similar to their retroviral counterparts, certain HERV-derived proteins also induce an innate immune response. TLR4 detects the HERV-W envelope protein to upregulate the expression of pro-inflammatory cytokines that may contribute to multiple sclerosis [188]. In contrast to L1 RNA, HERV RNAs are prone to forming dsRNAs because of the flanking bidirectional promoters in the LTR region, thus inducing a strong innate immune response. Treatment with a DNA methyltransferase inhibitor (DNMTi) induces an innate immune response through the activation of retrotransposons, which is thought to occur via the MDA5-MAVS and TLR3 pathways mediated by HERV dsRNA detection [21,23]. As TLR3 induces an innate immune response via HERV, the RNA/DNA hybrid formed during reverse transcription is also a potential immunogen. HERV-mediated immune responses have been implicated in several neurodegenerative diseases, such as amyotrophic lateral sclerosis and multiple sclerosis [189,190]. In addition, activation of HERV-K by the CRISPRa system results in slower cell growth and an increase in the expression of senescence markers, suggesting that HERV-K may drive senescence. The immune response induced by HERV-K intermediates may be the cause of the increased senescence rate [161].

Retrotransposons RNA degradation and sequestration

Retrotransposons and their hosts have competed in the evolutionary arms race for millions of years. Throughout evolution, hosts have developed multiple layers of inhibition to keep retrotransposons at bay and maintain genome integrity. Detailed descriptions of known retrotransposon inhibitors have been reviewed [3,191]. Retrotransposon expression induces innate immune responses, therefore, it is expected that the downstream pathway of innate immunity to express interferon-stimulated genes (ISGs) inhibits retrotransposon activities [96,153,192,193]. Indeed, multiple ISGs have been reported to inhibit retrotransposition; our mass spectrometry of the L1 ORF1p complex revealed a network of ISGs that interact and inhibit L1 retrotransposition [96], which includes the previously reported L1 inhibitors, dsRNA-specific ADAR1 [194], MOV10 RNA helicase [129,131,195], and zinc-finger antiviral protein (ZAP, ZC3HAV1) [192,196]. To reduce the immunogenicity of IRAlus, ADAR1 edits Alu RNA through A-to-I RNA editing, thereby avoiding the detection of immunogenic Alu by ZBP1 [197–199]. Although ADAR1 inhibits L1 retrotransposition, this inhibition is independent of ADAR1 editing activity, with an unknown mechanism [194]. Other examples of retrotransposon inhibitors include MOV10, which inhibits L1 retrotransposition by recruiting terminal uridylyltransferases as discussed in the previous section [129], and TREX1, which degrades retrotransposon cDNAs [154]. While RNase H2 has been suggested to degrade L1 RNA from L1 RNA/DNA hybrids, this specific RNA degradation may facilitate, rather than inhibit, L1 retrotransposition, perhaps by enabling more efficient synthesis of second-strand L1 cDNA [107]. This challenges the opposite hypothesis, where RNase H2 inhibits L1 retrotransposition, and suggests a more complex role for RNase H in the L1 life cycle [200]. The loss of RNase H2 enzymatic function may induce innate immune responses [201,202]. However, it remains unclear whether immunogenic retrotransposon-derived RNA/DNA hybrids are RNase H2 substrates.

To search for L1 RNA/RNP-specific regulators, we compared the L1 ORF1p RNA-binding-defective mutant to the wild-type L1 ORF1p by mass spectrometry analysis of the L1 ORF1p complex. Among the newly identified ISGs, we characterized the exonuclease protein helicase with zinc finger 2 (HELZ2), which degrades L1 RNA and reduces innate immune response levels. HELZ2 contains a conserved 3' to 5' exonuclease RNB, two helicase domains, and a zinc finger region that may target RNA viruses [96,203]. HELZ2 specifically recognizes the 5' UTR region of L1 RNA; consequently, removal of L1 5' UTR abrogates the HELZ2 recognition of L1 RNA. While it is unclear if the 5' UTR region of L1 RNA contributes to the immunogenicity, the region has the highest mutation rate in L1 sequences. One example is the mutation in the 5' UTR region to evade the zinc-finger protein ZNF93, which inhibits older L1 subfamilies, such as L1PA3, L1PA4, L1PA5, and L1PA6 [22]. HELZ2 may recognize specific RNA structures for degradation; thus, understanding the interaction between host factors, such as HELZ2 and retrotransposons may provide insights into the underlying mechanisms that contribute to the immunogenicity of retrotransposon-derived RNAs.

Conclusion and outstanding questions

Retrotransposons are genetic parasites that increase their copy number by copy-and-paste mechanisms, while evading host defence. Their impacts on genome diversity as well as DNA damage-mediated stress responses have been well documented. Recent discoveries strongly support the idea that retrotransposon intermediates can influence innate immune responses independent of retrotransposition, increasing interest in understanding of sterile inflammation that may contribute to autoimmune disorders. Although retrotransposons have coevolved with their hosts, some forms remain immunogenic, suggesting an ongoing battle with the host and/or that the host may adopt retrotransposons as a strategy to amplify the strength of the immune response.

Outstanding questions

(1) Innate immune response: It is still unclear whether the innate immune response towards retrotransposon intermediates is adopted and conserved in the host, or if the host recognizes these intermediates as a 'danger' signal. Further studies are required to elucidate whether this response is central to immunity or merely a host response towards an 'invader'.
(2) Contribution to inflammatory diseases: The extent to which retrotransposons contribute to inflammatory diseases remains uncertain. Although NRTi treatments in mice have shown promising results, more studies are needed to understand the impact of

retrotransposons on these diseases, and whether modulating retrotransposons could be beneficial to patients.

By addressing these questions, future research could lead to a better understanding of the complex interaction between retrotransposons and the host immune system including the evolutionary arms race, potentially leading to new therapeutic strategies such as modulating retrotransposon expression. For instance, acute upregulation could enhance the efficacy of cancer immunotherapy, while downregulation might help mitigate inflammation.

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Author contributions

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