ANNUAL REVIEWS

Annual Review of Genetics

The Epigenetic Control of the Transposable Element Life Cycle in Plant Genomes and Beyond

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Annu. Rev. Genet. 2022. 56:63–87

The *Annual Review of Genetics* is online at genet.annualreviews.org

https://doi.org/10.1146/annurev-genet-072920-015534

Keywords

transposable element, transposon, silencing, epigenetics, sequence domestication

Abstract

Within the life cycle of a living organism, another life cycle exists for the selfish genome inhabitants, which are called transposable elements (TEs). These mobile sequences invade, duplicate, amplify, and diversify within a genome, increasing the genome's size and generating new mutations. Cells act to defend their genome, but rather than permanently destroying TEs, they use chromatin-level repression and epigenetic inheritance to silence TE activity. This level of silencing is ephemeral and reversible, leading to a dynamic equilibrium between TE suppression and reactivation within a host genome. The coexistence of the TE and host genome can also lead to the domestication of the TE to serve in host genome evolution and function. In this review, we describe the life cycle of a TE, with emphasis on how epigenetic regulation is harnessed to control TEs for host genome stability and innovation.

1. INTRODUCTION

The term transposable element (TE) is broad and encompasses a diverse set of DNA sequences that are able to move from one location in a genome to another through a process called transposition (**Figure 1*a***). TEs include autonomous elements, which encode the proteins necessary to

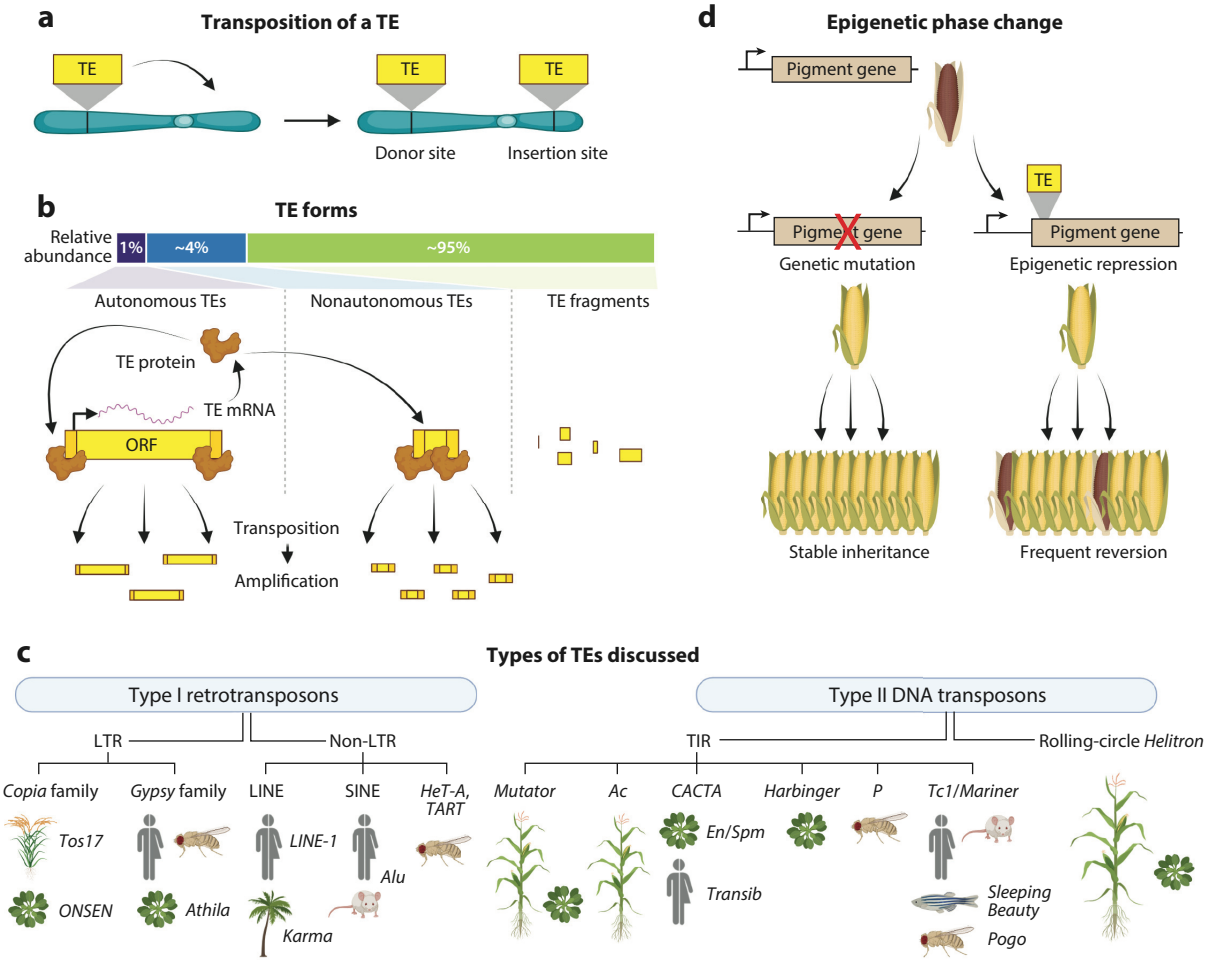


Figure 1

TE nomenclature. (*a*) Schematic of the basic process of transposition. This example is a copy-and-paste mechanism that results in a TE copy at both the donor and insertion sites, increasing the overall TE copy number. (*b*) Three major forms of TEs with mechanisms shown below: autonomous, nonautonomous, and fragments. Autonomous TEs encode the proteins that are able to catalyze their own transposition, as well as the transposition of nonautonomous elements that retain the functional TE protein-binding sites. Nonautonomous TEs can transpose, but are reliant on protein production from the autonomous TE. TE fragments are recognized as originating from the same TE family by the similarity of the DNA sequence but do not encode TE proteins and cannot transpose. The average relative percentage of each form in a typical genome family is shown. (*c*) Family types and relationships between the TEs discussed in this article. Type I retrotransposons duplicate through an RNA intermediate, which they reverse transcribe into a complementary DNA molecule. Type II DNA transposons directly mobilize the DNA sequence without reverse transcription. See the sidebar titled How Transposable Elements Get Their Names. (*d*) An example of the higher frequency of phenotype reversion associated with TE regulation compared to more stable genetic mutations. Abbreviations: *Ac*, *Activator*; LTR, long terminal repeat; mRNA, messenger RNA; ORF, open reading frame; TE, transposable element; TIR, terminal inverted repeat. Figures adapted from images created with BioRender.com.

transpose themselves; nonautonomous elements, which require protein production from an autonomous element of the same family to mobilize; and a much larger number of TE fragments, which are not able to transpose but can be recognized as originating from the same TE family (**Figure 1*b***). The types of TEs are further split between DNA transposons, where a DNA sequence is mobilized, and retrotransposons, which are mobilized in the RNA form before being reverse transcribed back into the genome (**Figure 1*c***). Retrotransposons are not excised from their original donor locations and therefore transpose via a copy-and-paste mechanism (for example, see **Figure 1*a***). DNA transposons excise via a cut-and-paste mechanism during transposition, but in some scenarios the TE sequence can be copied back into the donor position off a sister chromatid or a homologous chromosome, thus causing it to appear as if the DNA transposon was copied and pasted.

1.1. Discovery

TEs were famously discovered in the early 1950s by Barbara McClintock (95), who received the Nobel Prize for this work much later in 1984. Between the TE discovery and the award, McClintock continued to investigate different aspects of TE regulation. In 1964, McClintock (96) recognized that the activity of TEs alternates in an irregular pattern between active and inactive states. She coined the term "phase change" for TE expression states, which was characterized by a high propensity for reversion (**Figure 1*d***). Classical genetic mutations revert to their previous wild-type states very infrequently, as a rare second mutation is required to suppress the first mutation. McClintock found that revision was much more common in her system. McClintock was not observing genetic changes that revert but rather (transcriptional) activity states of the TE that would switch, be heritable for some time, and then switch back again. This high reversion rate is a hallmark of epigenetic phenomena, where the expression activity of a TE is heritable yet frequently reverts (see **Figure 1*d***) without an underlying change in the primary DNA sequence.

1.2. TEs Are a Mutagenic Force

Evolution is impossible without polymorphism, and TEs have been enormously successful at generating mutations and providing evolution with new genetic material. TE transcriptional activity results in transposition, which itself can lead to the insertion of the TE copy into a gene, mutating the gene's function. In addition, transposition creates breaks in the DNA, which are often not repaired seamlessly, generating new mutations. The process of transposition therefore generates mutations of single genes via insertion of TE copies, as well as other rearrangements (inversions, duplications, and translocations) that produce large-scale chromosomal variation (73, 151). Unfettered TE activity results in widespread genome damage and eventual sterility (43, 74). To prevent this genome damage as a consequence of transposition, organisms use an array of mechanisms to repress TE protein production (see Sections 1.3 and 1.4). Without any TE activity, new mutations (particularly structural variation) accumulate at a reduced level, slowing the rate of raw variation to be selected upon (17).

1.3. Modification of TE Chromatin

In eukaryotic organisms, TE activity is repressed at the transcriptional level by an array of chromatin modifications. These chromatin marks include posttranslational modification of histone tails [particularly methylation of histone H3 at the lysine 9 position (H3K9me)]; alternative isoforms of the histones themselves; and, in mammals and plants, the methylation of cytosine DNA bases (reviewed in 28, 135). TE chromatin can exist in at least two states: the transcriptionally repressed heterochromatic state with the above-mentioned modifications or the euchromatic

state (including chromatin that is unmarked or marked with active chromatin modifications), where TE promoters are active and expression occurs. Rather than exhibiting a simple binary switch, TEs can also exist in partial-activity states between these two polar endpoints and have other transcriptionally repressive chromatin modifications such as H3K27me (26), as well as be subject to environmental, stress, and tissue-specific regulation similar to the diverse array of gene regulation (see Section 4).

Two distinct mechanisms trigger heterochromatin modifications. First, compared to genic transcripts, TE transcripts are preferentially degraded into small RNAs that include small interfering RNAs (siRNAs) and related PIWI-interacting RNAs (piRNAs) (51, 72, 108). These two types of small RNAs not only trigger the degradation of additional copies of TE messenger RNAs (mRNAs) (leading to posttranscriptional gene silencing) but also target the heterochromatin modifications discussed above (104, 115, 130, 155, 156). Second, in vertebrates, Krüppel-associated box zinc finger proteins (KRAB-ZFPs) provide a transcription factor–based mechanism for silencing TEs (reviewed in 12). KRAB-ZFPs possess a variable array of zinc fingers that enables them to bind DNA in a sequence-specific manner. The TE-bound KRAB domain then recruits KAP1, which serves as a scaffold for recruiting chromatin-modifying proteins (10, 12, 128). Both the small RNA–based mechanism and KRAB-ZFPs lead to chromatin modification, heterochromatin formation, and transcriptional repression of the targeted TE DNA. These silencing mechanisms differ between organisms due to the constant arms race between the TE and host that leads to the rapid evolution of new pathways (**Figure 2**).

1.4. Epigenetic Regulation of TEs

Some chromatin modifications can be propagated across cell division, and therefore the placement of these marks can repress TE activity over long periods of growth. One key difference exists for the heritable epigenetic repression of TEs in plants versus in animals. In plants, epigenetic repression that occurs in one plant is likely to be passed *trans*-generationally and result in subsequent generations of TE repression (reviewed in 49). This strong *trans*-generational epigenetic repression is likely why McClintock observed it so clearly through her work in maize. In animals, chromatin-level silencing still occurs across mitotic divisions (as it does in plants), but in each generation TE repression is reset during gametogenesis or embryogenesis (145, 156). In invertebrate animals such as *Caenorhabditis elegans*, *trans*-generational epigenetic repression is performed by the inheritance of small RNAs (141), similar to the original targeting of chromatin modifications in plants (see Section 3). There are examples of *trans*-generational epigenetic inheritance in mammals, but these seem to be the rare exceptions rather than the rule (49). Nevertheless, epigenetic repression of TE activity is a constant, and the difference is only if, when, and how the resetting occurs.

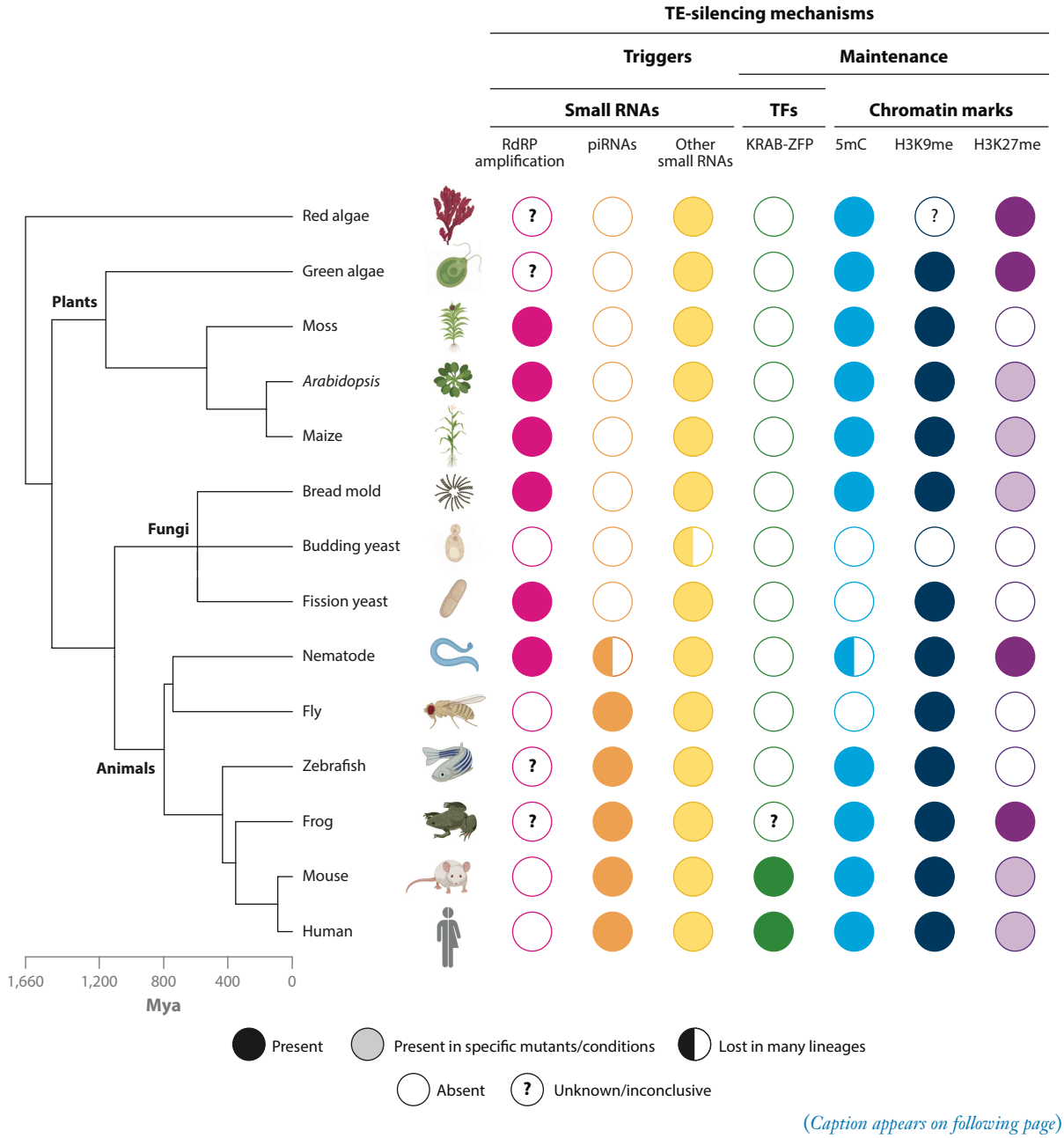
2. LIFE CYCLE OF A EUKARYOTIC TE

Although all known eukaryotes carry TEs in their genomes, both TE content (families and diversity) and abundance vary widely across species (reviewed in 142). This variability can be attributed to what point in the TE life cycle that particular host genome is at for each individual TE family present in the genome. This section serves as a roadmap and overview for the life cycle of a TE (**Figure 3**), with the other sections diving deeper into the epigenetic aspects of the TE life cycle.

2.1. Origin of the TE Life Cycle by Horizontal Transfer

The TE life cycle begins with the transfer of a TE into a new genome (**Figure 3**). The ability of TEs to insert themselves into the chromosomal DNA of another species is called horizontal

transfer (HT). The earliest evidence of TE HT came from the study of *P* elements in *Drosophila* (24). Since then, HT events have been identified for a variety of TE classes in many other species, including plants, invertebrates, vertebrates, and mammals (4, 33, 42, 58, 83, 109, 137). In particular, *Tc1/mariner* DNA transposons have been the source of hundreds of independent HT events in vertebrates (150). Since it is very difficult to catch an HT event in process and because these events happen on the evolutionary timescale, in the laboratory researchers studying the initiation of the TE life cycle often use the transgenesis of a foreign TE copy into a new genome to mimic



(*Caption appears on following page*)

Figure 2 (*Figure appears on preceding page*)

Evolution and conservation of TE-silencing mechanisms, including the presence or absence of seven major TE-silencing chromatin modifications and mechanisms during the evolution of the fungal, plant, and animal kingdoms. (*Top*) The pathways are split into triggers of TE silencing or mechanisms of chromatin-level maintenance of silencing. RdRP amplification refers to the presence of siRNA populations that are amplified through the action of an RdRP enzyme (117, 140, 157). The evolution of a new pathway is often paired with the corresponding loss of another, for example, the piRNA system's replacement of RdRP siRNAs. By contrast, the mechanism of H3K9me is a conserved TE-silencing chromatin mark for nearly all eukaryotes. Light-shaded H3K27me circles refer to cases in which this chromatin mark is not typically associated with TEs but is recruited to them upon TE reactivation and/or the loss of another pathway (26, 48). Abbreviations: 5mC, DNA base cytosine methylated at the fifth carbon position; H3K9me, methylation of lysine 9 in histone H3; H3K27me, methylation of lysine 27 in histone H3; KRAB-ZFP, Krüppel-associated box zinc finger protein; Mya, million years ago; piRNA, PIWI-interacting RNA; RdRP, RNA-dependent RNA polymerase; siRNA, small interfering RNA; TE, transposable element; TF, transcription factor. The phylogenetic tree was constructed using TimeTree (76). Figure adapted from images created with BioRender.com.

the natural process of HT (37). The mechanism and consequences of HT are discussed in more depth in recent reviews (41, 142).

2.2. Period of TE Activity in a Naive Host

Once in a new genome, in theory the TE will have a period of unfettered activity and amplification (**Figure 3**). This assumes that the TE is autonomous, properly transcribed, and translated in its new environment and that the other host-encoded proteins required for it to transpose are present

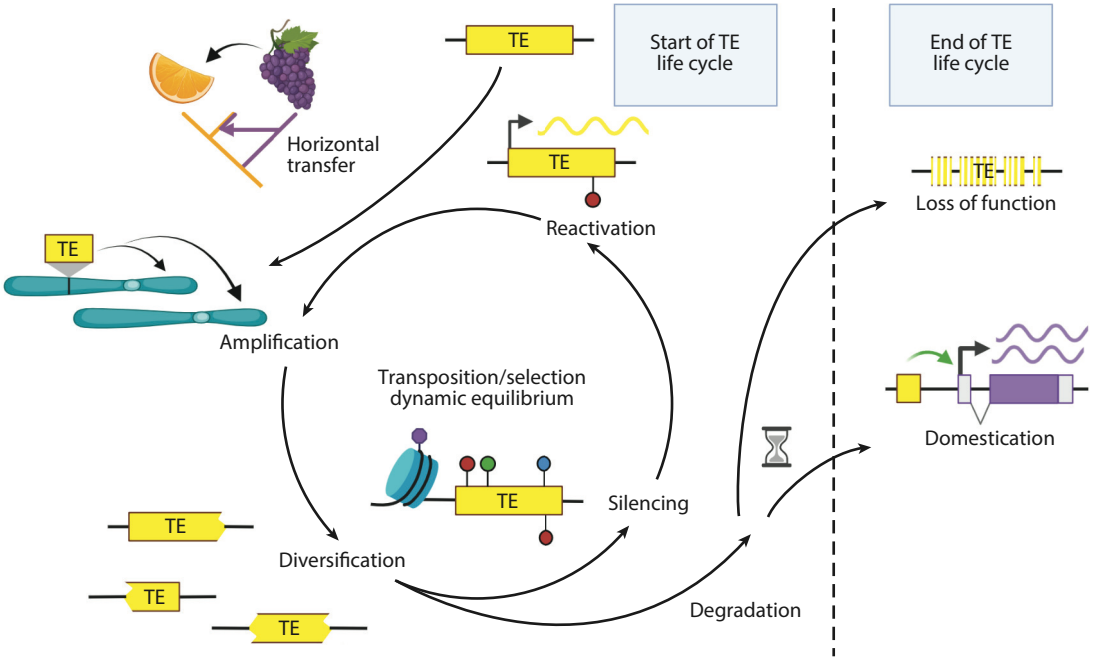


Figure 3

Summary of the transposable element (TE) life cycle. The TE life cycle begins with the transfer of a TE into a new genome. This invasion can be followed by a period of TE activity in the naive genome that results in the amplification of TE copies and the diversification of TE sequences. This diversification can lead to the TE being triggered for epigenetic silencing. At this point, the TE can escape silencing, reactivate and amplify more, and come to a dynamic equilibrium of activation and repression with the host genome. Alternatively, the TE life cycle can progress to the end (*dashed line*) either by repurposing the TE via sequence domestication for host genome function or by the loss or destruction of all autonomous elements. Each of these processes is discussed in this review. Figure adapted from images created with BioRender.com.

and available. If able to transpose, in theory the TE exists in an environment that has not yet adapted or developed the mechanisms to trigger its epigenetic silencing. This would cause a period of TE activity, mobilization, mutagenesis, increase in copy number, and diversification of the TE sequences (**Figure 3**).

2.3. End of the TE Life Cycle by Sequence Degradation

Over the evolutionary timescale, accumulation of deleterious mutations and loss of TEs from the genome lead to the end of the TE life cycle. Most simply, through genetic segregation or mutation, a genome or species can be left without an intact autonomous element, rendering that TE family unable to transpose and thereby leading TE sequences to slowly degrade (**Figure 3**). Since the activity of TEs is dependent on the transposition enzymes that are encoded from the open reading frames (ORFs) inside the autonomous TEs, mutations in these ORFs lead to dysfunction of transposition enzymes and will destroy the TE's ability to create new functional copies.

Several mechanisms of mutation destroy TEs. First, TEs are subject to the same replication-based errors and point mutations as the rest of the genome. Second, TE sequences can be removed by the process of illegitimate or ectopic recombination. In plants, illegitimate or ectopic recombination between retrotransposons belonging to the same family has been predicted to cause TE deletions and subsequent reduction of the genome size (29, 89). Comparative studies of primate genomes have also identified ectopic recombination as a potential mechanism for the precise removal of many small *Alu* elements (85). The high copy number of nearly identical TE copies makes them particularly susceptible to illegitimate recombination. Third, the process of transposition itself often leads to the generation of new variant TE copies (see Section 3). For example, imperfect transposition can fracture a full-length autonomous element into a nonautonomous element or TE fragment (**Figure 1*b***). Combined, all three mechanisms of TE mutation are responsible for the fact that the majority of TEs in any given genome are transposition-incompetent fragments (**Figure 1*b***).

As a unique example of targeted TE mutation, in *Neurospora crassa* and several other fungi species, mutations can be specifically driven to TEs through the mechanism of repeat-induced point (RIP) mutation (reviewed in 38). This mechanism detects duplicate TEs based on homologous DNA–DNA interactions and triggers cytosine-to-thymine mutations (15, 44). As in the above cases, mutating all of the autonomous elements will again leave the TE family without the ability to transpose and lead to the end of the TE life cycle.

2.4. TE Epigenetic Silencing

In contrast to the TE life cycle ending via degradation, a second pathway exists that results in temporary and tunable repression of TE activity and a high chance of reactivation. A TE or TE family can be epigenetically silenced, which provides the ability for the TE to reactivate at a later time (**Figure 3**), similar to the example of frequent phenotype reversion from **Figure 1*d***. TEs can provide an evolutionary force to shape genome plasticity, and therefore this epigenetic silencing strategy may be preferred when organisms need to maintain the silenced state of TEs in the short term but then reactivate them when mutations or transcriptional rewiring is later needed.

When an active TE has accumulated to a high copy number, this copy number buffers against the end of the TE life cycle due to sequence degradation. Due to TE amplification, there may be so many intact elements and functional TE protein-coding ORFs that a high number of genetic mutations would be required to halt TE activity. Instead, a faster way to repress TE activity, particularly for a high-copy-number TE family, is to trigger its epigenetic silencing, which would repress all elements in the genome at once. The triggering of TE silencing is discussed in Section 3.

2.5. Epigenetic Maintenance of the Silenced State

Although our understanding of the initiation of TE silencing is limited (see Section 3), the maintenance of DNA methylation and/or histone modifications during cell division, and thus the epigenetic inheritance of the silenced expression state, is well studied (reviewed in 49). In plants, the DNA methylation associated with TE silencing can be faithfully propagated for more than 30 generations (7) and methylation can act to *trans*-generationally maintain TEs in a silenced state until the erosion of their sequences (see Section 2.3), reactivation (see Section 2.6), or domestication (see Section 5). Multiple pathways have been found to maintain DNA methylation, including DNMT1 (MET1 in plants) for CG sequence context DNA methylation, the plant-specific CMT3 for CHG methylation, and CMT2 for CHH methylation (H = A, C, or T) (reviewed in 149). An additional well-studied protein required for the maintenance of TE silencing is the chromatin-remodeling protein LSH1 (DDM1 in plants). Loss of function of MET1 and DDM1 leads to a decrease of DNA methylation, H3K9me, nucleosome condensation, and other key chromatin modifications necessary for the maintenance of genome-wide TE transcriptional silencing, leading to widespread TE transposition (100, 101). During this reactivation, other pathways attempt to compensate and resilence the TEs [including the small RNA and H3K27me pathways (27, 106)] but cannot resilence the TE over a long-term period without these key maintenance factors.

2.6. Reactivation

To avoid the end of the TE life cycle by sequence degradation, TEs use several mechanisms to escape from silencing (reviewed in 84). In one mechanism, a TE family may be reactivated during an HT or hybridization event where a previously absent autonomous element enters the genome and provides the ability for the TE family to transpose again. An interesting example of this type of reactivation is the *Sleeping Beauty* element (see the sidebar titled How Transposable Elements Get Their Names), which was reconstructed in the laboratory based on an estimation of what the autonomous element must have looked like in fish, and then was able to transpose in a new genome (59). In a separate mechanism, even without the addition of new elements, TEs that have been silenced for generations can occasionally escape silencing and transpose again. The evidence for TE escape from silencing can be detected on the evolutionary timescale by analyzing almost

HOW TRANSPOSABLE ELEMENTS GET THEIR NAMES

The naming of transposable elements (TEs) is disorganized and fractured (see **Figure 1*c***). For many years researchers were free to name a newly discovered element whatever they liked. Some elements are named for acronyms, such as LINEs (long interspersed nuclear elements). Other TEs are named for one key characteristic of the TE, such as *Sleeping Beauty* (because it was resurrected from inactive fragments) or *ONSEN* (Japanese for hot spring due to its temperature regulation). Some TEs are named to evoke anthropomorphized movement around the genome: *Harbinger*, *Mariner*, or *Pogo*. Confusingly, sometimes two or more of these naming systems are used simultaneously, such as the *hAT* transposon family (*hobo* from *Drosophila*, *Ac* from maize and *Tam3* from snapdragons).

There have been several efforts to restructure TE naming in a logical manner. For example, a system has been created to name individual elements using a three-letter code that signifies TE type and position in the genome (DTM023421 = DNA transposon, TIR-type, *Mutator* family, next to gene #023420) (143). Other efforts have included adding a two-letter species code before the TE name to signify the host genome (ZmDTM023421 for *Zea mays*). Lastly, efforts are rightfully underway to change the names of some TEs that are derogatory, such as *Gypsy* elements.

any eukaryotic genome. Duplicated TE sequences can be used to date the timing of transposition, and time periods of TE amplification bursts in copy number can be detected. Using these methods, we know when, in which TE families, and in what genomes TE escape from silencing has occurred. However, the specific mechanism by which the TE reactivated and escaped silencing is often unclear, and there are likely many mechanisms that can lead to this escape (discussed in Section 4).

Some reactivated TEs have escaped or evaded silencing and are still active today, such as the *LINE-1* retrotransposons in the primate lineage (71). Other TEs that were once silenced can be resilenced again after a period of activity. This generates the past burst in TE copy numbers that can be observed for long terminal repeat (LTR) retrotransposons in grass genomes (8). The research field has not been able to differentiate the mechanisms that resilence TEs from those that originally silence the TE (discussed in Section 3), so to our current knowledge these mechanisms of silencing and resilencing are the same. See Section 4 for a more detailed description of TE escape and resilencing.

3. THE INITIATION OF TE SILENCING

Although it seems counterintuitive, the examples known to initiate TE epigenetic silencing are first triggered by genetic changes. In these cases, the genetic change in DNA sequence occurs at a single element in the genome but has downstream epigenetic effects on the activity level of the rest of the TE family. There are several examples in the literature where a single individual trigger element begins to produce small RNAs, which then function in *trans* to target chromatin modifications to any region that has sequence similarity to the small RNA. This process has been termed "identity-based silencing" (37), and the major concept is that sequence changes at one individual element have the potential to repress the entire TE family. In this way, the Achilles' heel of TE activity may be the high number of transposed elements and the inaccuracy of those transposition events and locations where they insert, which provides an environment that is highly likely to spawn elements capable of triggering the downfall of the entire system.

3.1. Production of a Poisonous Derivative Element

Transposition is often an imperfect process that creates deletions, inversions, and duplications of both the TE and the flanking DNA. During transposition or illegitimate recombination, derivative TE copies can be generated. These mutations can turn an autonomous element into a nonautonomous derivative or a nonmobile TE fragment (see Section 2.3). In most cases, the production of the derivative element does not influence the rest of the TE family. However, in some rarer cases, a derivative element is generated that acts as a poison element copy and is able to trigger the epigenetic silencing of the rest of the TE family. The primary example of this regulation is the maize *Mu killer* element, which formed during an abortive transposition of the autonomous element (134). The derivative element that was formed is a long inverted repeat of the TE, which is located downstream of a genic promoter. This promoter expresses the inverted repeat into double-stranded RNAs, which in turn are cleaved into siRNAs. These siRNAs then act to target DNA methylation and transcriptionally repressive histone modifications to the entire *Mutator* TE family (133) via the plant pathway termed RNA-directed DNA methylation. The key aspect that makes *Mu killer* such an efficient silencing trigger is that the gene's promoter expressing the inverted repeat is upstream of the siRNA-generating region and therefore insulated from becoming silenced itself as it continues to generate transcripts and siRNAs (134). *Mu killer* triggers the domino effect that results in the transcriptional epigenetic silencing of the other *Mutator* elements, which then are inherited to the progeny and maintained in their *trans*-generationally silenced state without

the need for *Mu killer* to constantly retrigger silencing. Similar *killer* poison elements derived from deleted and rearranged single elements have also been described for different TE families such as *Activator* (*Ac*) (139).

3.2. Transposition into a TE Trap

In addition to derivative elements triggering silencing, intact (unmutated) single elements can trigger silencing by transposing into regions of the genome that are recalcitrant to TE activity. In this case, a TE family can remain active in the genome until a single element transposes into a position that not only triggers the silencing of this individual element but again starts the domino effect of generating small RNAs that work in *trans* to silence the rest of the TE family. For example, the TE may transpose into a piRNA cluster, which is a graveyard of fragmented TEs that generates piRNAs (90, 126). As with the above example of *Mu killer*, the key is that the transcription necessary to constantly generate the piRNAs is controlled outside and upstream of the TE and piRNA cluster, so it does not silence itself but rather continues to generate piRNAs (45). Once located in the piRNA cluster, the trapped element becomes the master repressor of this TE family and is free to erode, with the only constraint being that it needs to retain enough sequence complementarity with the rest of the TE family members to keep them repressed. The *Drosophila flamenco* element is the primary example of the TE trap concept, as it is located in a piRNA cluster and acts to repress an entire *Gypsy* TE family (148). In this way, piRNA clusters, and knobs or centromeric regions in other genomes, can be thought of as islands of degraded TEs that the cell uses for identity-based silencing with the function of repressing the activity of full-length TEs located in other regions of the genome.

4. ESCAPE AND RESILENCING

TE epigenetic silencing is not necessarily a one-way street. Silenced and tamed autonomous TEs can escape silencing from the host genome and become active again (135). Several escape mechanisms have been discovered and are discussed below. Although these escape mechanisms have been studied, a major unanswered question in the field is how TEs that were already present and silenced in a genome become reactivated over long evolutionary periods. These bursts in TE activity can be detected in the sequences of genomes today and dated to a narrow period of activity that played a major role in reshaping an organism's genome. We now understand that reactivation of already-present TEs occurs at different times, even for TEs within the same genome (25). This suggests individual element or TE family-level dynamics rather than global reactivation of all TEs at once.

4.1. Position-Dependent Activation

The position of a TE in a genome is highly correlated to its activity state and future potential to transpose (reviewed in 131). For a given TE, insertion into heterochromatin may not only result in silencing but also act to maintain the TE's silenced state (see Section 3.2). Conversely, a different outcome could occur for TEs inserted into euchromatic intergenic regions or regions adjacent to essential genes. Neighboring gene expression could lead to activation of the TE, keeping it associated with active chromatin marks and preventing silencing (**Figure 4*a***). For example, the *Arabidopsis Mutator* TE can escape silencing when it inserts itself into the 3′ untranslated region (UTR) of an essential gene (66). Another example from this same TE family in a different organism highlights the effectiveness of the TE's strategy to target insertion into genic promoters and UTRs (30). The *Mu killer* trigger for epigenetic silencing (discussed in Section 3) can effectively inactivate autonomous *Mutator* elements, which usually remain silenced even after *Mu*

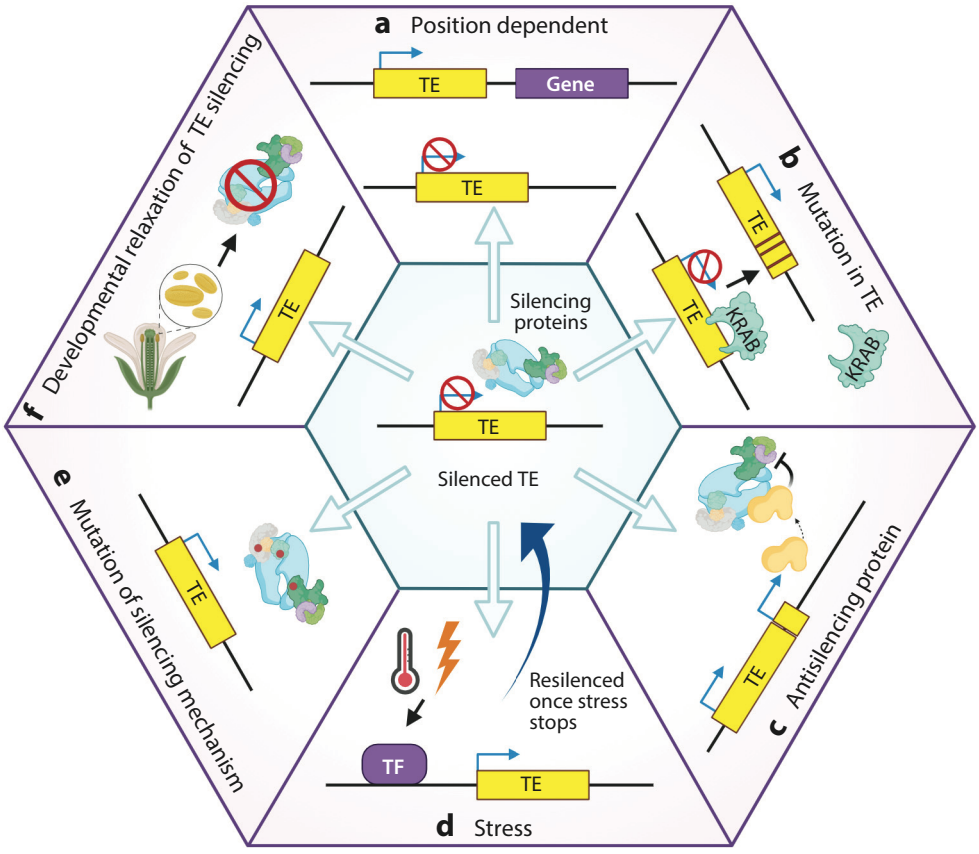


Figure 4

Escape from epigenetic silencing. Six mechanisms of TE reactivation, starting with an epigenetically silenced autonomous TE (*center*). On the single TE level, the TE may be influenced by neighboring gene regulation and reactivated in a process of position-dependent activation (*a*, *top*). In addition, individual TEs may mutate to avoid being recognized by silencing mechanisms (*b*), or the TE itself could generate a new antisilencing protein to inhibit the silencing process (*c*). Stress may also temporarily reactivate TEs through stress-responsive transcription factors, which regulate either the TE itself or neighboring genes that influence the adjacent TE (*d*). In the case of stress activation, the TE is typically resilenced once the stress is alleviated. More globally, TEs may reactivate due to mutations in the host silencing mechanism (*e*) or when silencing factors are not expressed during specific tissues or time points in a process called "developmental relaxation of TE silencing" (*f*). Abbreviations: KRAB, Krüppel-associated box; TE, transposable element; TF, transcription factor. Figure adapted from images created with BioRender.com.

killer segregates away (133). However, the activity of one particular *Mutator* element is reactivated after *Mu killer* is segregated away due to the active chromatin state of a specific insertion site in the 5′ UTR of a conserved gene (132) (**Figure 4*a***). In this manner, TEs that target genic regions of the genome (such as many type II DNA transposons) may have an evolutionary advantage that makes them more likely to reactivate. Organisms would be unlikely to sacrifice the normal function of essential genes in order to repress the interloping TE.

4.2. Drift of TE Sequences

The accumulation of mutations in TE sequences may allow TEs to escape repression by the host (60) (**Figure 4*b***). In this manner, the identity-based silencing systems that operate through siRNA/piRNA complementarity may no longer match the drifted TE sequence. Foreign TEs that

are moved into new genomes, either in the laboratory or by the rare process of HT, are known to be able to transpose in the naive genome for a period of time before their silencing is triggered (see Section 2). In a similar manner, sequence drift may make the endogenous TE different enough to avoid KRAB-ZFP binding and repression.

4.3. Evolution of New Features to Evade Silencing

A few TEs have evolved antisilencing systems to specifically avoid being repressed (**Figure 4*c***). Through the process of DNA acquisition, sequences are regularly incorporated into TEs. These acquired sequences may be used for a new function (different from their original evolutionary purpose), leading to TE mobilization or helping the TE escape the host systems that repress its activity. Many TEs encode proteins of unknown function, and some of these proteins may aid in TE activity, similar to the way that many viral proteins act to suppress host viral defense mechanisms (2). For example, the *En/Spm*-encoded protein TnpA in maize, the *Harbinger* transposon-derived proteins, and the VANC protein in *Arabidopsis* function as antisilencing factors (32, 52, 56). To date, similar antisilencing systems have not been identified beyond plants (22).

4.4. Acquisition of Tissue and Stress Sensitivity

TEs can also acquire DNA sequences that act as enhancers to promote expression of the TE during very specific spatial, temporal, or stress conditions (**Figure 4*d***). TEs have long been known to reactivate during plant or animal tissue culture (50, 67, 114). In fact, it was common for many years for researchers to purposely mutagenize rice populations by passing the plants through tissue culture, where the *Tos17* retrotransposon would reactivate, create new phenotypes, and tag these genes with TE sequences for simplified identification of the causal gene (50).

Various biotic and abiotic challenges, including environmental stress and hormone treatment, can activate TEs (14, 57, 62, 86). The *ONSEN* TE from *Arabidopsis* captured a heat-activated *cis*-regulatory element in its promoter region (55), resulting in a natural heat-inducible TE transposition system. The heat-induced *ONSEN* TE displays an insertion site preference for developmentally regulated genes, and the new insertions of *ONSEN* directly influence the transcription of these newly targeted genes (125). This suggests that *ONSEN* can rewire the gene expression network of developmental genes during heat stress. *ONSEN* transcripts diminish during the recovery period following heat stress treatment, indicating that the reactivation of this TE is temporary.

ONSEN is an example of TE-specific control rather than global reactivation. Recent studies have shown that the effects of stress alone on TE reactivation are limited, but combining the stress with a weak allele or mutation in the silencing system results in a powerful activation of TEs in the lab (55) and in wild populations (5). This suggests that stress may not result in broad activation of TEs but may prime or sensitize the system in individuals with a weakened silencing system.

4.5. Mutation or Loss of the Silencing System

A different type of mechanism of TE escape involves the mutation or loss of a key silencing factor from the host genome (**Figure 4*e***). An example is the loss of a key factor in the RNA-directed DNA methylation machinery in certain wild populations of *Arabidopsis* (70). This loss of silencing machinery is expected to affect a wide range of TEs (i.e., global reactivation), in contrast to the above examples that only regulate one element or TE family at a time. For example, in animals (including humans), age-dependent activation of TEs has been widely reported, and this may be due to the lack of expression of a key silencing factor (34, 47, 81). In the *Drosophila* brain, several TEs become highly active during normal aging, leading to an impairment in neuronal function (81). Wood et al. (144) showed that the lifespan of *Drosophila* is increased by blocking TE

activation, suggesting that the activation of TEs is at least partially responsible for age-related neuronal decline. Researchers have suggested that TE activation is due to the age-dependent decrease in AGO2 function (81). AGO family proteins bind small RNAs and carry out the activity of small RNA–based translational, posttranscriptional, and transcriptional regulation of TEs (91). In these cases, TE activation may be an effect of a tissue-specific genome-wide loss of repressive protein factors that function to maintain silencing, resulting in TE activation.

In plants, developmental relaxation of TE silencing has been characterized in various tissues, including two nutritive nurse tissues: the pollen grain vegetative cell and endosperm (53, 136). In the pollen vegetative cell, this loss of maintenance-level TE repression is associated with a developmentally programmed loss of heterochromatin (13) (**Figure 4*f***). Therefore, a genome-wide activation of TEs occurs at specific developmental stages in both animals and plants. Determining the downstream function of developmental TE activation and how these events contribute to cell fate change are major questions to be addressed in the future.

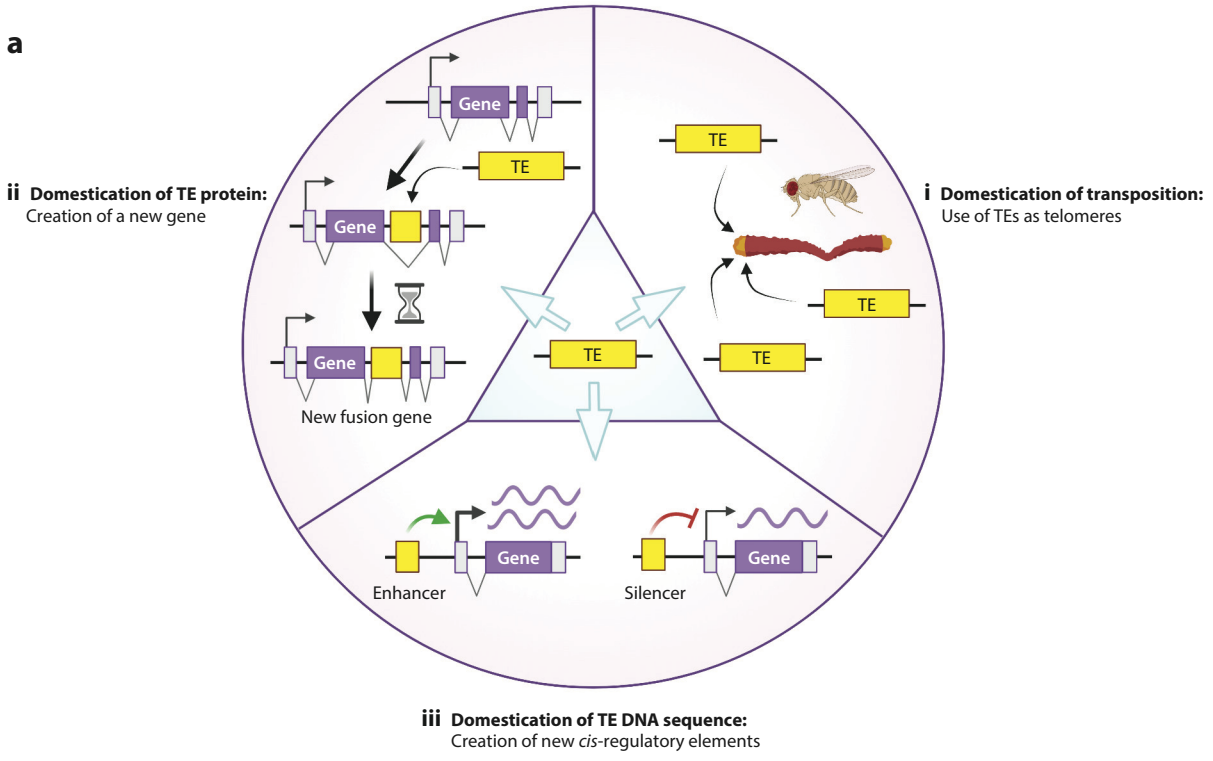
Although the mechanism remains unclear, the reactivation of TEs in hybrids may be due to a similar loss or inhibition of the host silencing system. Wide hybridization events, which can occur in both plants and animals, result in the reactivation of TEs (64, 99, 129). This genome-wide level of TE activation in some hybrids suggests a change in the host system of TE repression rather than an activation of individual elements. These wide hybridization events are associated with a global loss of DNA methylation (153), and although the mechanism at work is not clear, this phenomenon may be related to a haploinsufficiency or global repression of a key silencing factor in the hybrid.

5. TAMING TES BY REUSE AND DOMESTICATION

In addition to the loss of TE activity via sequence degradation or epigenetic silencing, an alternate route exists that leads to the end of the TE life cycle. This alternate route no longer puts the TE's activity in conflict with the host genome but instead harnesses the TE's unique molecular capabilities for the benefit of the host. Thus, a natural end of the TE's life cycle is to be repurposed or domesticated by the host genome into a beneficial tool that performs a function for the cell/organism. A TE element or family may blend with the host genome, domesticating some aspect of TE behavior or sequence to generate emergent properties that no one individual TE has but that the TE-derived system now plays a key role in. There are a number of ways that TE sequences and/or functions can be domesticated to prove their worth and thereby be subject to positive selection. We distinguish TE domestication events by three main categories: domestication of (*i*) transposition, (*ii*) TE proteins, and (*iii*) TE sequences or fragments (**Figure 5*a***).

5.1. Domestication of Transposition

TEs can be domesticated by repurposing the functional transposition activity performed by the TE proteins. Domesticated TEs can retain their ability to transpose, but in a controlled manner to benefit the cell. For example, in insects of the order Diptera, the telomerase gene was lost during evolution (92). In nearly all eukaryotes, telomeric sequences are composed of short repeats synthesized by telomerase enzymes, and without this function chromosomes would progressively shorten during DNA replication, creating genome instability. Diptera replaced telomerase function with two specialized non-LTR retrotransposons, *HeT-A* and *TART*, which play a critical role in telomere maintenance and integrity (40). These TEs transpose in a controlled fashion to the chromosome ends, extending the sequence and balancing the rate of chromosome shortening (**Figure 5*a***, subpanel *i*). In this case, TE activity has been domesticated to prevent chromosome instability.



(*Caption appears on following page*)

Figure 5 (*Figure appears on preceding page*)

Domestication and reuse of transposable elements (TEs). (*a*) Examples from each of the three major routes of natural TE domestication. (*i*) The transposition function of the TE may be repurposed, with the example of telomere extension in *Drosophila*. (*ii*) The TE proteins may be domesticated for a host genome function or combined with existing proteins into new genes. (*iii*) The TE DNA may act as a binding site for proteins that influence neighboring gene expression, repurposing the TE as an enhancer element. (*b*) Examples of human influences on the TE life cycle. (*i*) The human influence of the industrial revolution resulted in moths that were no longer camouflaged by their backgrounds. A TE-induced mutation resulted in dark-pigmented moths that better fit their new environment (138). (*ii*) The human-selected diversification of canines is associated with the activity of SINE nonautonomous retrotransposons (46). (*iii*) Humans have selected against TE activity while breeding for crop uniformity (112, 152). (*iv*) Humans have used TEs as tools, including via the inexpensive method of tagmentation, which transposes adapter sequences into DNA in order to create deep-sequencing libraries (1, 116). Figure adapted from images created with BioRender.com.

The most archetypal case of the domestication of transposition in vertebrates is the V(D)J recombination reaction that takes place during lymphocyte development. The *Transib* TE family was domesticated to use TE excision events in a specific region of the genome as a diversity-generating mechanism to produce a large number of different antibodies (68). The transposase proteins RAG1 and RAG2 remove fragments of the genome, rearranging the DNA sequence and providing the raw diversity to be able to encode the millions of possible antibody combinations required, but only perform these excision events in limited immune cell types. Similarly, domestication of entire TE systems has occurred in prokaryotes through the fusion of DNA transposons and Cas-like genes to generate casposons involved in the development of CRISPR-Cas prokaryotic adaptive immunity systems, with the benefit of integrating new genetic information into the bacterial genome (75).

A final example of host-beneficial transposition is the resistance (*R*) genes of plants, which function to recognize pathogen molecular patterns and set off a cascade of gene expression responses. *R* genes are packed into gene clusters, and these clusters have a higher proportion of TEs compared to the rest of the genome (79). *R* gene clusters are highly variable and change more rapidly than the rest of the genome, which is at least partially due to the presence of TEs in these regions. Therefore, the TEs may impart these genome regions with the higher mutation rate needed to prevail during the evolutionary arms race with the pathogen. In this case, the plant does not have strict control over the transposition mechanism as in V(D)J recombination, but it harnesses the TE's ability to mutate and rearrange these key gene clusters as a diversity-generating mechanism. Domestication of the entire functional transposition system is likely evolutionarily rarer than domestication of TE fragments (see Section 5.3); nevertheless, domesticated transposition systems represent critical diversity-generating mechanisms for both eukaryotic and prokaryotic cells.

5.2. Domestication of TE Proteins

TE-encoded proteins can be domesticated for purposes other than transposition, such as DNA binding. In these cases, the TE-encoded protein no longer performs the transposition or retrotransposition reaction but is neofunctionalized to take on a new role for the cell. For example, the domestication of the full *Mutator* transposase protein gave rise to FAR1/FHY3 transcription factors that are essential for the plant light response (82). In primates, the GAG protein from *Gypsy* retrotransposons has experienced distinct domestication events that have driven the formation of gene families involved in placentation and brain development (11, 35, 111). Similarly, domestication events of the ENV protein from the human endogenous retrovirus (*HERV*) have generated various *Syncytin* genes, which play a key role in cell-to-cell fusion during placental development (80).

Domestication can also occur by the fusion of TE-derived proteins with host proteins (**Figure 5*a***, subpanel *ii*). Fusions between TE-derived proteins and additional host protein

domains can create chimeric proteins and enzymes with novel functions. An example is the SETMAR protein, in which a primate *Mariner* transposase sequence is fused to a SET domain protein (21). This new enzyme confers two distinct new functions: (*a*) chromatin regulation via histone methyltransferase activity and (*b*) a distinct mechanism of DNA repair. In the case of TE protein fusion, the propensity for TEs to capture or copy host DNA and incorporate it into the TE facilitates the formation of new combinations (23, 63). In addition, the inaccuracy of transposition of a TE into a gene may result in element fusion. These chimeras are likely nearly all nonfunctional or deleterious, but examples from the literature demonstrate that in rare cases they can provide the host cell with a new useful function and be selected for.

As illustrated in the examples above, TEs have repeatedly been domesticated to serve in specific pathways, such as in placental formation/function and chromatin regulation. For example, TE-derived *Pogo* genes were domesticated to play an important role in heterochromatin assembly and chromosome segregation (36, 93), and the domestication of *Mutator* transposases and *Gypsy* LTR retrotransposon proteins contributes to the condensation of pericentromeric heterochromatin (54). Since TEs are the genome-wide targets of heterochromatin formation (see Section 1.3), their proteins may be predisposed to function in this pathway once domesticated.

5.3. Domestication of TE Sequences as Regulatory DNA

TE sequences can be domesticated for their use as regulatory elements that act as drivers or repressors of transcription and can rewire single-gene or large-scale gene regulatory networks. For example, the TE fragment may provide a protein-binding sequence that influences the regulation of a nearby gene (**Figure 5*a***, subpanel *iii*). Some elements can be repurposed as *cis*-regulatory elements that act as tissue-specific enhancers or transcription factor–binding sites (reviewed in 39, 122). As an example, nonautonomous MITE elements have captured transcription factor–binding sites and mobilized these enhancer elements upstream of new genes (102). Because MITEs are small, transpose often, and regularly incorporate new fragments of DNA, they have played a key role in the genome-wide distribution of enhancer sequences.

Domesticated TE sequences that act as enhancers contribute to entire networks of tissue-specific gene expression, stress response, and disease resistance. In human embryonic cells, TEs constitute up to 20% of the binding sites of OCT4, NANOG, and CTCF, which are key regulators for pluripotency (77). In plants, ~2,500 MADS-box transcription factor–binding sites overlap with *Helitron*-domesticated TE sequences and play a key role in endosperm development (6). There are numerous examples of TE sequences being domesticated into enhancer elements and becoming important in placentation (19), pregnancy (88), neocortex development (105), and liver development (65). In plants, enhancer formation from TE sequences has contributed to resistance to aluminum (113), cold, and salt stress (103). The ability of TEs to rewire entire gene expression networks is explored further in other recent reviews (18, 22).

5.4. Domestication of TE RNAs

In addition to acting as promoter regulatory elements, TE fragments can directly impact the post-transcriptional regulation of a gene's RNA. For example, an *Alu* element insertion in the *TBXT* gene is the main driving force for tail loss during ape evolution (146). This new *Alu* insertion created a fold-back transcript isoform, which alters RNA processing and, when tested in mice, was sufficient to produce the tail-loss phenotype. In a second example, a TE insertion into the intron of the *cortex* gene in moths (*Biston betularia*) increased the expression of a specific transcript isoform and conferred the dark pigmentation necessary for better camouflage in their changed environment during the industrial revolution (138) (**Figure 5*b***, subpanel *i*).

Besides affecting the processing of genic mRNAs, TE sequences are the origin and targets of multiple long noncoding RNAs (lncRNAs). For example, ~15,000 human lncRNAs have been reported to contain TE sequences (69). A specific example is the *HERVH* LTR-derived lncRNA, which is required to maintain pluripotency in human embryonic stem cells (123). In plants, ~50% of lncRNAs are associated with a TE origin (16) and a subgroup of these has an impact on abiotic stress in maize (87).

TE fragments can also generate microRNAs, siRNAs, or piRNAs that regulate genes (reviewed in 98). From plants to humans, there are many microRNAs derived from TEs that function to regulate gene expression (118, 119, 121). TEs are also the source of some gene-regulating siRNAs. For example, the *Arabidopsis Gypsy* element *Athila* encodes siRNAs that match the *UBP1b* gene, which is the homolog of TIA-1, an essential protein for the formation of stress granules (97). When *Athila* is active and attempts retrotransposition, its transcripts are sequestered, and translation is inhibited by stress granules. By coding *UBP1b*-matching siRNAs, *Athila* represses its own repressor, generating the proteins required for retrotransposition.

5.5. Formation of Epialleles

TEs are subject to chromatin modifications (see Section 1.3) and also may be domesticated (see above). These two aspects can be combined to bring the domestication event under chromatin-level control. In this way, genes can be subject to epigenetic control due to their incorporation of TE sequences (**Figure 5*a***). This epigenetically controlled gene is called an epiallele, since this allele is subject to the TE's epigenetic regulation. Examples exist where the regulation of the gene is subject to the same chromatin-level, developmental, stress-induced, or disease-induced regulation of the TE. Epialleles are well studied because they represent examples of unusual gene regulation. The phenotypes they cause often do not follow cell lineage or normal inheritance patterns and frequently revert. For example, the yield of oil palm fruit is affected by an epiallele (107). The non-LTR retrotransposon *KARMA* is located in an intron of a gene that controls sexual organ development. This gene has two epialleles: methylated (Good *KARMA*) and unmethylated (Bad *KARMA*). The Bad *KARMA* epiallele causes an alternatively spliced transcript, which results in fruit devoid of oil. The Good *KARMA* and Bad *KARMA* epialleles rapidly switch between states, necessitating constant assaying of *KARMA* methylation levels. This highlights a key characteristic of epialleles: their ability to switch/revert expression states much faster than genetic mutations.

The formation of epialleles may represent an early stage of TE domestication, when the TE-derived region is still subject to the regulation of the rest of the TE family. At later stages of domestication, the TE-derived sequence may be cut down in size and the regulation may be refined to the point that it no longer matches the regulation of the rest of the TE family from which it came, resulting in loss of the epigenetic control of gene regulation.

6. CONCLUSION: HUMAN INTERACTIONS WITH THE TE LIFE CYCLE

We have detailed several natural mechanisms that can result in the loss or reactivation of activity during the TE life cycle. However, we should not overlook the interaction between human influence and the TE life cycle. TE activity is responsible for many of the milestone mutations that propelled human thinking; for example, TEs provided Mendel with his wrinkled pea seeds (9) and turned moths dark to match soot-covered trees during the industrial revolution (138) (**Figure 5*b***, subpanel *i*). Conversely, bacterial TEs have enabled the development of antibiotic-resistant strains (110), which have become an important public health concern.

Without knowing how or what we are doing, human desire has provided pressure for the rapid selection (120) of particular states of the TE life cycle, in some cases for TE activity and in other cases for inactivity. For example, species that humans have had success domesticating into diverse varieties may have only had the potential to become domesticated in the first place due to the innate activity of TEs in the original strains, generating the raw variability required for selection. The rapid expansion and diversification of SINE elements in dog breeds (46) (**Figure 5*b***, subpanel *ii*), specific horizontal gene transfer in cheese-making fungi (124), and the high TE diversity in the wild ancestor of tomatoes (31) may be why these species were malleable to human pressures for different morphologies while others were not. By contrast, examples exist where humans have applied selective pressure for a lack of TE activity and the end of the TE life cycle. Many seed crops, which are bred for uniformity and consistency, have immobile TE systems and are not capable of generating new TE-induced mutations. In these cases, without understanding what they were breeding out, humans selected against the functional autonomous TEs and removed them from the genome (31, 112, 152) (**Figure 5*b***, subpanel *iii*).

Today, as we continue to indirectly select for particular activity states of the TE life cycle, we are now also directly harnessing the TE's unique abilities for our use. We use TEs to generate insertion mutant lines as a resource for functional genomics (20, 78, 94, 127) and have engineered the production of inexpensive deep-sequencing libraries by using the TE's ability to transpose library adapter sequences into DNA in an in vitro process termed tagmentation (1, 116) (**Figure 5*b***, subpanel *iv*). In addition, some cancer therapies are based on TE-related endogenous retroviruses (61), the *Sleeping Beauty* transposon system is being tested for clinical applications and gene therapy (3), and the TE-derived CRISPR-Cas system has revolutionized how scientists approach biological questions (147, 154).

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors thank Todd S. Macfarlan for helpful discussion of KRAB zinc finger proteins. P.L. is supported by grant IOS-2149964 from the US National Science Foundation. D.C.-G. is supported by a William H. Danforth Plant Science Fellowship from the Donald Danforth Plant Science Center and the Nuevo León State Fellowship from Mexico's National Council of Science and Technology. S.S. is supported by a fellowship from the Life Sciences Research Foundation and Simons Foundation. This work is supported by grant MCB-1904326 from the US National Science Foundation to R.K.S.

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Annual Review of Genetics

Volume 56, 2022

Contents

Errata

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