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Review

From the cauldron of conflict: Endogenous gene regulation by piRNA and other modes of adaptation enabled by selfish transposable elements

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ABSTRACT

Transposable elements (TEs) provide a prime example of genetic conflict because they can proliferate in genomes and populations even if they harm the host. However, numerous studies have shown that TEs, though typically harmful, can also provide fuel for adaptation. This is because they code functional sequences that can be useful for the host in which they reside. In this review, I summarize the "how" and "why" of adaptation enabled by the genetic conflict between TEs and hosts. In addition, focusing on mechanisms of TE control by small piwi-interacting RNAs (piRNAs), I highlight an indirect form of adaptation enabled by conflict. In this case, mechanisms of host defense that regulate TEs have been redeployed for endogenous gene regulation. I propose that the genetic conflict released by meiosis in early eukaryotes may have been important because, among other reasons, it spurred evolutionary innovation on multiple interwoven trajectories - on the part of hosts and also embedded genetic parasites. This form of evolution may function as a complexity generating engine that was a critical player in eukaryotic evolution.

1. Introduction

In sexually reproducing species, genetic conflict arises when there is competition among genetic elements over transmission across generations. A key example of genetic conflict is provided by transposable elements (TEs), genetic elements that encode instructions for making copies of themselves. Genetic conflict arises because TEs can increase within genomes and across generations even if they cause harm [1]. TEs come in two major flavors defined by their mode of replication. DNA transposons move via a DNA-intermediate and are further classified as either cut-and-paste transposons or helitrons. Cut-and-paste transposons encode a transposase that enters the nucleus, recognizes the DNA element, excises it and inserts the DNA element elsewhere. Copy number increase of cut-and-paste transposons occurs when they land in front of a replication fork or when the DNA breaks that they leave behind are refilled with the same sequence via homologous recombination from allelic or non-allelic copies. Helitrons are believed to amplify through rolling circle replication, a form of replication whereby continuous replication of a circular DNA molecule spins off many single-stranded copies. Retrotransposons are the second main flavor of TE and also come in two forms. Long-terminal repeat (LTR) retrotransposons encode a reverse transcriptase and replicate through reverse transcription (RT) of transcribed mRNA in the cytoplasm. LTR retrotransposons share many similarities to infectious retroviruses and can make capsid/virus-like particles (VLPs) but commonly lack the envelope protein (ENV) that would make them infectious. LTRs that carry ENV are also known as endogenous retroviruses. non-LTR retrotransposons (also known as LINEs) are a second class of retrotransposon that lack LTRs. They also replicate through RT, but instead the RT reaction occurs in the nucleus and is primed from the target genomic DNA sequence.

Why does sexual reproduction release genetic conflict in the form of TE proliferation? Bacteria that lack sexual reproduction carry TEs, but not to the same extent as eukaryotes. Eukaryotes are all derived from an ancestor capable of meiosis and TEs more rapidly increase in sexually reproducing species because fertilization allows TEs to move from one genome and colonize another [1]. Sexual reproduction also facilitates TE proliferation because recombination separates replicating TEs from their harmful consequences. If a TE copy causes a lethal mutation, the original TE insertion will be removed from the population through tight linkage to the lethal allele it was responsible for. However, if recombination separates the original copy from the lethal allele, the original copy will be unencumbered by the harm it caused. In asexuals lacking genetic exchange, a proliferating TE lineage will drive its own extinction by being bound to the mutations that it causes. It will become locked within an increasingly damaged host genome and these hosts will be at a competitive disadvantage against hosts without the proliferating TE [2,

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3]. However, if fertilization allows continued transmission to new genomes and recombination separates a TE from the mutations it causes, TEs can proliferate even if they reduce population host fitness [4]. Thus, meiosis that originated in early eukaryotes releases genetic conflict with TEs.

The idea that TEs represent genetic parasites was established in the early 1980 s by Orgel, Crick, Doolittle, Sapienza, Hickey and others [1, 5–9]. However, prior to that, some believed that TEs instead might have been generally beneficial. In fact, Barbara McClintock, who discovered TEs through their capacity to affect gene function, believed that they had a critical role in the developmental regulation of gene expression [10–12]. Early models of developmental gene regulation also suggested that the large abundance of repetitive DNA in animal genomes could be explained by gene regulatory function [13,14]. Truly, TEs have not persisted *because* of the benefit they provide to the host. But it is clear that Barbara McClintock was partly correct. Since natural selection has

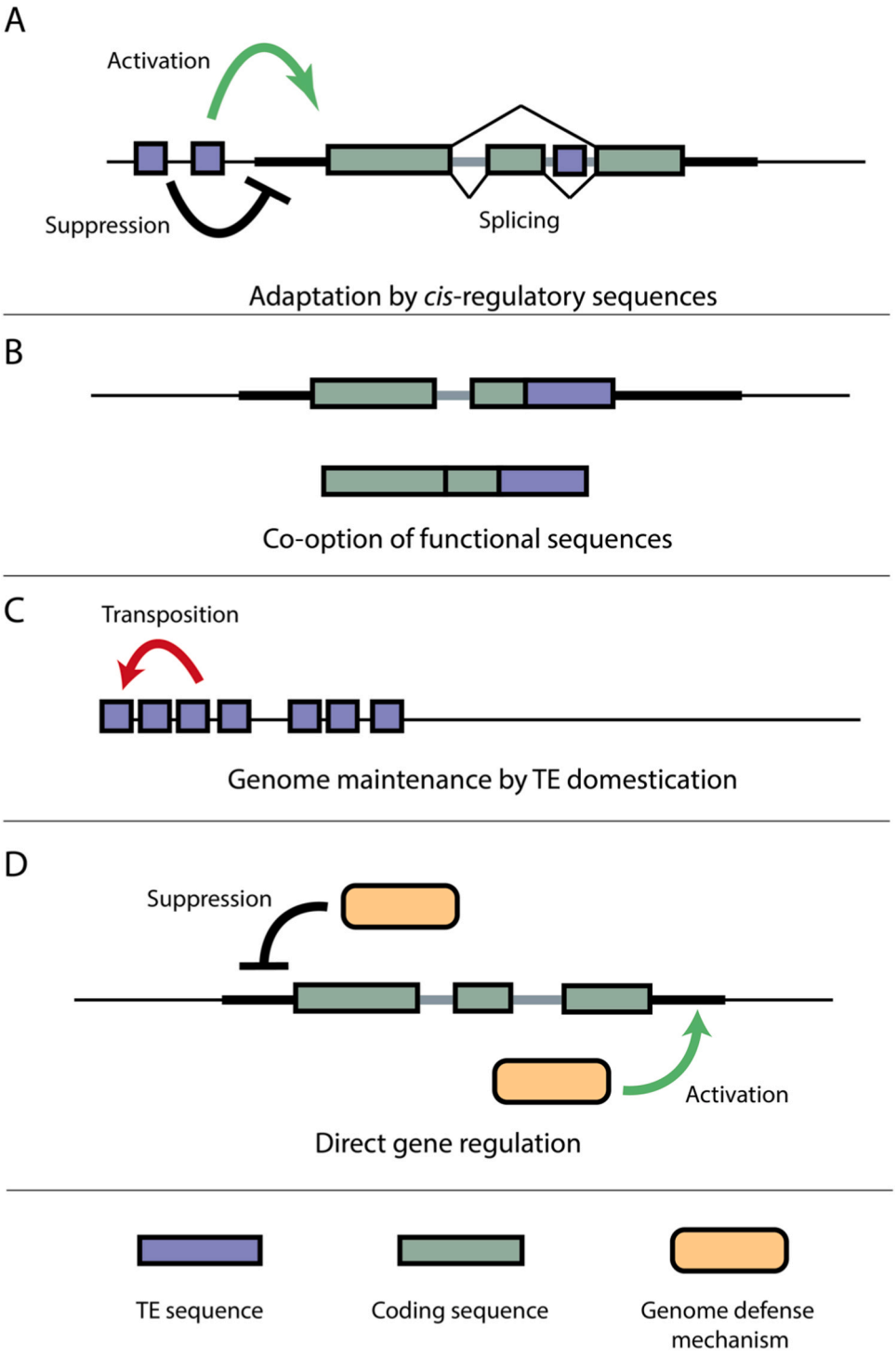


Fig. 1. A) Mode 1: Host adaptation by TE *cis*-regulatory elements. TE insertions can either activate or suppress gene expression or alter splicing. B) Mode 2: Co-option of functional sequences. TE sequences can code for protein sequences that are functional for the host. C) Mode 3: Genome maintenance by TE domestication. Actively proliferating TEs can be domesticated for genome maintenance. D) Mode 4: Host repurposing of genome defense pathways for endogenous gene control. Systems of genome immunity that evolved under genetic conflict can be repurposed for gene regulation, either through activation or suppression.

an uncanny ability to make do with whatever happens to be lying around the genome [15], it appears that TEs *can* act as the controlling elements that McClintock envisioned, though perhaps not to the degree she proposed. And while it doesn't explain their origin and success, it is clear that TEs can have a special role in adaptive evolution.

What is the special role that TEs have in adaptation? Several modes of TE co-option have been clearly documented. For single TE insertions, these are either regulatory or functional. A third mode of co-option is not driven by individual insertions, but rather through the act of proliferation itself. These three modes of TE-enabled adaptation have been well reviewed [16–21], so I will not do so extensively here. In this review I wish to describe a fourth and indirect mode of adaptation enabled by host-TE genetic conflict. In this fourth mode, TEs do not directly provide the novel variation that is selected. Rather, adaptation is mediated through redeployment of host-TE control mechanisms for gene regulation. This mode of adaptation is therefore indirectly enabled by genetic conflict. In this case, conflict drives the origin and maintenance of a defense machinery that is then repurposed for non-defense function. In this review, I seek to outline both how and why genetic conflict with TEs can provide critical fuel for adaptation through these four different modes, with a focus on the role of piRNA silencing in the fourth mode.

2. Modes of direct host adaptation mediated by TEs

2.1. Mode 1: Host adaptation by TE cis-regulatory elements

An important mode of host adaptation is through co-option of *cis*-regulatory elements carried by TEs. As TEs proliferate, they spread copies of themselves throughout the genome of their host. Like any gene, these elements must carry regulatory sequences that recruit RNA polymerase to drive their expression in a manner that enables their proliferation. Since evolution is a tinkerer [15], these regulatory sequences can also be useful for the control of host gene expression on the part of the host.

The degree to which these regulatory sequences provide fuel for adaptation likely depends on the strategies employed by the TE in the context of host biology. In plants, somatic stem cells have the capacity to differentiate into germline tissue and new TE insertions in somatic tissue can be transmitted across generations. For this reason, regulatory sequences that drive TE expression in somatic cells can enable TE proliferation in plants across generations. Thus, as expected, TE *cis*-regulatory co-option can also play a role in plant somatic function [22]. For example, TEs appear to play a role in shaping the plant stress response. In maize, a large number of genes that are responsive to stress have flanking TEs that trigger this response [23]. This is attributed to the fact that TEs themselves are stress-responsive and carry stress response regulatory sequences [24–28]. Why would a TEs carry stress responsive elements? Stress-responsive regulatory control may increase the chance for vertical or horizontal transmission [24]. For the *ONSEN* LTR element, heat induction is likely a TE evolutionary strategy to trigger activation in dividing cells, especially cells of the meristem. Thus, hijacking the host heat stress response can enhance its own proliferation [29].

In contrast to plants, most animals have a sequestered germline. For this reason, TEs residing in most animals are proposed to carry regulatory elements specialized for expression in this unique part of the animal [30]. In this case, co-option of TE-encoded *cis*-regulatory elements for the control of gene expression is expected to be more common in tissues where TE expression is optimal for TE proliferation. In plants, this would include somatic tissues. But in animals, this would be within the germline or early embryo prior to germline sequestration.

Studies in mammals are consistent with some of these predictions. For example, numerous studies have shown that endogenous retroviruses carry regulatory sequences that drive expression in the very early embryo, enabling an increase in copy number that is transmitted to the next generation. In mice, the endogenous retrovirus MuERV-L is one of the earliest zygotically transcribed genes [31]. In humans, different endogenous retroviruses are dynamically expressed at distinct stages of early development and this early expression in undifferentiated cells is enabled by transcription factors that play key roles in maintaining pluripotency by regulating cellular differentiation and self-renewal [32]. NANOG and Oct4 are two critical pluripotency transcription factors and a number of ERVs and other TE families carry NANOG and Oct4 binding motifs [33]. In mice, humans and primates, endogenous retrovirus sequences play a role in the developmental regulation of genes during early embryogenesis [34–39]. Functional analysis has also shown that *cis*-regulatory sequences provided by TEs are essential for the regulation of essential mRNA isoforms. For example, Dicer, a key factor in the biogenesis of miRNAs and siRNAs, has different isoforms in mice. One isoform is expressed only in oocytes and has greater double-stranded RNA cleavage efficiency. This increased efficiency is explained by an N-terminal truncation driven by an intronic retrotransposon expressed from its own promoter [40]. Another fascinating example of TEs playing a role in generating alternate isoforms is provided by cyclin-dependent kinase-2 associated protein 1 (*CDK2AP1)* [41] in mice. Similar to Dicer, a retrotransposon drives an N-terminal truncation and this isoform is necessary for proper mouse embryonic development. Interestingly, the isoform for murine *Cdk2ap1* that relies on this TE insertion is also present in humans, but the human isoform is instead driven by a promoter containing an L2a retrotransposon and a Charlie4z DNA transposon. This latter pair of TE insertions is conserved across eutheria. This indicates that while the isoform is evolutionary conserved, a new TE insertion has supplanted an earlier TE-based mechanism of isoform formation.

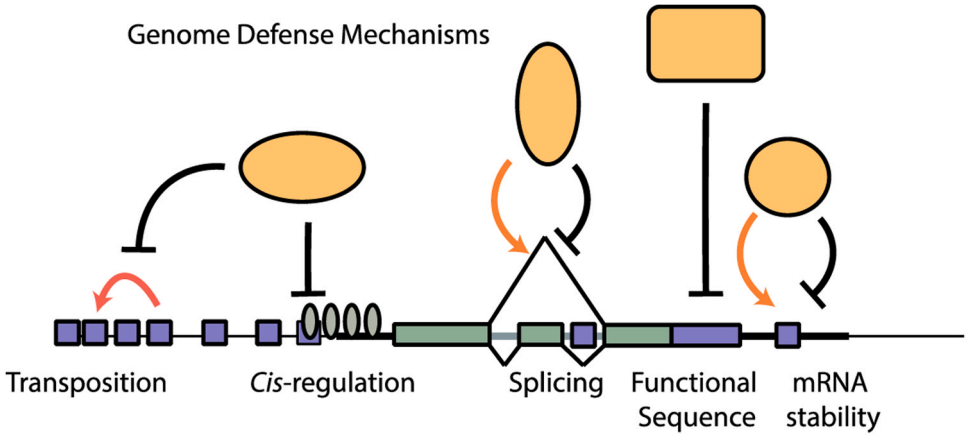


Fig. 2. Mixed modes of adaptation enabled by host-TE conflict. Here, genome defense mechanisms (in orange) mediate TE effects on gene function.

While theory might predict that TEs in animals with a sequestered germline would provide little fuel for *cis*-regulatory co-option for somatic function, this isn't entirely true. For example, endogenous retroviruses provide *cis*-regulatory control of a number of important genes expressed in the human placenta, which is presumably a dead-end tissue for TE proliferation [42–44]. In addition, as evident in plants, *cis*-regulatory TE sequences have been deployed for immune function and stress responses in a variety of animals [45–47]. This deviation from theory can likely be explained by several factors. First, natural selection may not be sufficient in honing the optimal animal TE strategy regulatory sequences, thus allowing "leaky" somatic expression. Second, optimal refinement of TE regulatory sequences may actually favor some somatic expression. For endogenous retroviruses that are infectious [48–50] and elements that exploit a strategy relying on frequent horizontal transfer [51,52] selection on the lineage may optimally drive expression in somatic tissues as a means to enhance proliferation beyond the host source.

2.2. Mode 2: Co-option of functional protein sequences

In addition to carrying regulatory sequences that drive TE expression, TEs also carry the critical machinery for making copies of themselves. In the case of cut-and-paste DNA transposons, the critical functions are coded by the transposase. This enzyme binds to repeat sequences that flank the TE, excises the element, recognizes a target site and mediates insertion at the new location. Retrotransposons, on the other hand, encode for multiple distinct proteins. Both LTR and non-LTR autonomous retrotransposons encode for reverse transcriptase, but they also encode other functions that enable their proliferation. For example, LINE-1 elements have two open reading frames that encode orf1p and orf2p. Orf2p encodes a reverse transcriptase that generates the LINE-1 cDNA [53] and an endonuclease [54] that cuts DNA at the site of insertion, together driving a target-primed reverse transcription reaction that inserts a copy at the target site. Orf1p is not present in all non-LTR retrotransposons [55], but provides nucleic acid chaperone function for the LINE-1 element [56–58]. LTR elements have a more diverse assemblage of protein functions [59], encoding *gag* (contributing capsid structural function), *pol* (contributing protease, reverse transcriptase and integrase function) and, in some circumstances, *env* (contributing envelope proteins that bind to cell surface receptors, thus mediating cell-cell transmission).

These diverse protein functions have provided useful variation and have been important for host adaptation. For transposases, both DNA binding and endonuclease function can be co-opted. In a systematic study of ~600 tetrapods, more than 90 independent host-transposase fusion events were identified [60]. An early identified example of a host-transposase fusion is the *SETMAR* gene in monkeys and apes, a fusion between a gene carrying a SET domain with histone methyltransferase activity and a *mariner* DNA transposon [61] that retains both DNA binding and nuclease function. *SETMAR's* DNA binding and nuclease function has been recruited for non-homologous end-joining repair [62–66]. By binding to broken DNA ends, *SETMAR* has a role in repairing double-strand breaks. In fact, overexpression of *SETMAR* increases resistance to ionizing radiation and enhances the efficacy of non-homologous end joining repair [63]. In bats, a *KRAB* domain transcriptional repressor [67] has also fused with a *mariner* DNA transposon that binds DNA [60]. This has led to the evolution of a new transcription factor that regulates several genes through interaction with flanking terminal inverted repeats derived from the active *mariner* transposon. Functional genes derived from DNA transposons have also been identified in plants. For example, the *DAYSLEEPER* gene from *A. thaliana* is a predicted zinc-finger derived from a *hAT* DNA transposon [68]. *In vitro* assays demonstrate that *DAYSLEEPER* has the capacity to bind DNA and the absence of functional *DAYSLEEPER* leads to aborted development in *A. thaliana*. Overexpression of *DAYSLEEPER* also alters gene expression, suggesting that *DAYSLEEPER* is an essential transcription factor.

Retrotransposons also have provided additional raw coding function co-opted by hosts. Interestingly, most known cases of functional co-option are provided by LTR retrotransposons rather than non-LTR retrotransposons. This may be explained by the fact that LTR elements code a greater diversity of proteins that mediate a more complex set of life-cycle functions within the host. Perhaps the most striking example of host co-option is the case of syncytins. In mammals, syncytins are named for their role in developing a single, multinucleate tissue (a syncytium) from cells at the surface of the embryonic blastocyst. The surface of the embryonic blastocyst consists of a layer of cells known as trophoblast cells. Fusion of these trophoblast cells into a syncytium forms a syncitiotrophoblast, a multinucleate cell mass that forms the boundary between the mother and fetus. Since this tissue is not composed of individual cells, the syncytiotrophoblast forms a protective boundary at the fetal-maternal interface [69]. Strikingly, the syncitins that mediate cell-cell fusion have been recurrently derived from *env* proteins encoded by endogenous retroviruses[70–73]. This recurrent co-option is driven by the fact that *env* proteins that mediate virus-cell fusion through host receptor binding can also mediate cell-cell fusion. A second property of LTR retrotransposons is the formation of a viral capsid by *gag* proteins. Both flies and tetrapods [74–77] have independently co-opted *gag* proteins from LTR retrotransposons as a means to transfer mRNA between cells of the nervous system. *gag* proteins build the viral capsid that contains viral RNA and these co-opted *gag* proteins can likewise encapsulate endogenous mRNA, which is then transferred to other cells via extracellular vesicles. Considering recurrent co-option of LTR proteins, it appears that their complex interactions with their hosts make them especially useful to have lying around the genome for evolution to tinker with [15].

2.3. Mode 3: Genome maintenance by TE domestication

In the previously described modes of adaptation enabled by genetic conflict, either regulatory or functional aspects of various TEs have been converted into host genes. In these cases, a single insertion provides benefit to the host, and this function was presumably selected at a single locus. In this process, these elements lose their capacity to proliferate. However, in some cases, the proliferative ability *itself* is recruited for host function. This represents a different mode of adaptation driven by genetic conflict. Interestingly, in contrast to Modes 1 and 2, the two most well understood cases for this mode of TE driven adaptation arise from non-LTR elements rather than DNA transposons or LTR retrotransposons. So far, this mode has only been well described in *Drosophila*, perhaps because insects carry a greater diversity of non-LTR elements compared to mammals. Additionally, since the excision of DNA transposons leaves unrepaired DNA breaks and LTR retrotransposons can be both infectious and produce harmful DNA in the cytoplasm [78], perhaps the continued proliferation of non-LTR elements is more tolerated by the host.

The telomeres of *Drosophila* provide the most well-known example of host function provided by continued TE proliferation. Rather than relying on telomerase, telomere ends in *Drosophila* are maintained by continued transposition of three different non-LTR families: TART, Het-A and TAHRE [79–82]. By maintaining preference for insertion into the telomeres, these elements can maintain chromosome ends that would normally be depleted by successive rounds of DNA replication. An analogous mode of genome maintenance by active TEs is seen in the example of R2 non-LTR elements that reside within the highly repetitive rDNA arrays of *Drosophila* [83]. R2 elements have been residents of these arrays for tens of millions of years across insects [84]. Due to their repetitive nature, the rDNA arrays are unstable and can undergo intrachromatid recombination leading to copy number loss. Counteracting this loss requires rDNA copy number increase within the germline and this is facilitated by R2 elements that provide double-strand breaks. Double-strand breaks induced by an active R2 lineage are proposed to

mediate homologous repair off sister-chromatids and unequal exchange. Unequal sister chromatid exchange with a repetitive locus can lead to an increase of copy number on one sister chromatid and a corresponding loss on the other sister chromatid. Thus, preferential retention of the sister chromatid carrying increased copy number within the germline stem cells can restore an rDNA array that has been depleted.

2.4. Mode 4: Host repurposing of genome defense pathways for endogenous gene control

Due to the damage they inflict upon genomes, a wide variety of TE suppression mechanisms have evolved and been maintained across eukaryotes. The main mechanisms of suppression are based on RNA silencing, chromatin silencing and DNA methylation. These systems are tightly interwoven across eukaryotes. For example, in plants, RNA silencing in the nucleus can trigger DNA methylation at transposon insertions through a process known as RNA-directed DNA methylation (reviewed in [85]). In mammals, Krüppel associated box (KRAB) zinc-fingers are a class of transcriptional repressors that can directly bind TE insertions and nucleate repressive chromatin (reviewed in [86]). Piwi-interacting RNAs (piRNAs) are a class of 23–30 nt RNAs that form a complex with Piwi proteins and mediate recognition of TE transcripts, targeting repressive chromatin at TE insertions in the nucleus or mediating transcript degradation in the cytoplasm (reviewed in [87–90]). These systems of TE repression have also been co-opted for host regulation of endogenous genes (reviewed in [91,92]). In this section, I will make the case that this has been a fundamental mode of adaptation enabled by genetic conflict by focusing on piRNA silencing as an example. At the base of the eukaryotic tree, meiosis established conflict in the genome. And while meiosis can play a critical role in generating new alleles and enabling adaptation, perhaps a secondary critical outcome was the development of new modes of gene regulation out of the cauldron of conflict itself (See Box 1).

2.4.1. The detectors and effectors of genome immunity against TEs

Immune systems provide defense against non-self agents and require two critical components. The first is a detector component that identifies harmful non-self agents. In systems of adaptive immunity, these correspond to antibodies. The second is the effector component that destroys or represses the non-self agent. How is detection of harmful non-self agents accomplished? Detection of harmful TEs may be classified as either ultimate or proximate detection. Ultimate detection can be defined as the first step in recognizing the non-self identity of a harmful agent and depends on the property of the agent that signals non-self identity to the host immune system. For TEs, ultimate detection systems typically recognize their Achilles heel - element mobility itself. Proximate detection can be defined as the mode of non-self detection, instructed by the ultimate detection system, that directly recognizes and targets the destruction of copies of the harmful agent.

In *Neurospora crassa*, ultimate detection is triggered by new TE insertions that are unpaired when chromosomes are aligned during meiosis [93]. Here, the ultimate detection system recognizes a proliferating element through its tendency, unlike genes, to lack a copy on the homologous chromosome. Through poorly understood mechanisms, the unpaired DNA becomes a source of small silencing RNAs that silence mRNA sequences corresponding to the unpaired sequence [94,95]. These small RNAs serve the purpose of proximate detection. In mammals, the HUSH complex ultimately detects TE insertions based on their lack of introns, which is a signature of having been derived through reverse transcription[96]. Finally, KRAB zinc-fingers both ultimately *and* proximately recognize specific sequences within elements that have a long period of co-existence within mammalian genomes[97,98]. This stands in contrast to recognizing a TE based on its TE mobility. Rather, recognition by KRAB zinc-fingers is an evolved strategy that depends on the specific sequence features of the element. In this section, I outline how piRNA silencing functions as an immune system to protect the genome, but has secondarily been co-opted for various modes of gene regulation (See Box 2). piRNA silencing provides an outstanding

Box 1
Which came first: the conflict or the reg(ulation)? The ancestral genome defense hypothesis.

One central assertion in this article is that adaptation arose from a system of RNA silencing whose original function was defense against viruses and selfish genetic elements. But RNA silencing, centered on Argonaute proteins, is also essential for regulating developmental genes by miRNAs. Which of these functions evolved first? Answering this question is essential for understanding how conflict with viruses and selfish genes influences adaptation. If a developmental role for RNA silencing arose first, and a defense function arose secondarily, we would need to reconsider how conflict itself influences evolution. Based on the conserved role of RNA interference in viral defense, it may seem likely that viral defense arose before miRNA function. But at least one miRNA appears shared between plants and animals [149], suggesting that the ancestral eukaryotic function of RNA silencing may have been for endogenous gene regulation by miRNA. Additionally, if miRNA function is not ancestral within eukaryotes, about nine different instances of the miRNA pathway would have evolved independently [150]. This seems, perhaps, unlikely. Nonetheless, Ago proteins, at the heart of eukaryotic RNA silencing against viruses and TEs, also have defense functions against plasmids and phage in prokaryotes [151,152]. Thus, it seems likely that the ancestral mode of eukaryotic RNA silencing was centered on immunity. But for other ancient modes of gene regulation, such as those based on chromatin and DNA methylation, we do not know whether their function in gene regulation evolved from an ancestral role in genome defense or vice versa. Some have argued that the ancestral function for these modes of gene silencing was originally rooted in protecting the genome from damage and these modes of epigenetic regulation actually allowed TEs to proliferate with reduced harm [153]. If so, then chromatin-based gene regulation and DNA methylation would not represent examples of host co-option of genome defense. Rather, TE control would have evolved from endogenous gene regulatory mechanisms. Alternatively, if the ancestral functions of chromatin and DNA methylation gene silencing were for genome defense, then these would represent additional examples of the fourth mode of adaptation enabled by conflict whereby defense mechanisms become re-deployed for gene regulation. A strong ancestral genome defense hypothesis proposes that the origins of RNA silencing, DNA methylation and chromatin-based gene regulation were all driven by defense against genetic parasites. In my view, the timing of the origin of meiosis supports this hypothesis. Meiosis was present within the last eukaryotic common ancestor. While this new mode of inheritance clearly sparked tremendous subsequent innovation, it would have also released genetic conflict *during* its evolution rather than after. Thus, it seems reasonable that the ancestral function of many core modes of eukaryotic gene regulation, such as RNA-silencing and DNA methylation, evolved from mechanisms that evolved to immediately suppress genetic conflict. This is based on the belief that selection to minimize the negative impact of agents that directly antagonize the host will be stronger than selection for fine tuning gene expression. Supporting this hypothesis, a recent investigation of highly divergent eukaryotes suggests that the ancestral function of Polycomb Repressing Complex 2, which has essential roles in development, was for TE repression [154] But future comparative studies across diverse eukaryotes are clearly needed to resolve this question of whether defense or gene regulation was the dominant pressure driving the evolution of these different modes of genome function.

Box 2
On the frequent recruitment of immune function for development.

In addition to the ways that genome defense has been recruited for host function, a number of other mechanisms of immunity have been also recruited in a developmental context. If the ancestral function of RNA silencing was for immunity (See Box 1, but also see [155]), then developmental regulation by miRNAs represents a striking example of adaptation derived from an immune module. But there are a number of additional examples whereby immune function has been repurposed for development. Proteins carrying Toll/interleukin-1/resistance gene (TIR) domains play a role in immunity signaling across animals, plants and bacteria, suggesting an ancestral immune function [156–159]. This ancestral function has subsequently been repurposed in Toll-like receptors for a variety of developmental functions in flies [160], nematodes [161], sea anemone [162] and also in mammals, where Toll-like receptors are important for nervous system development [163]. Another example of immune function repurposing is provided by the process of synaptic pruning mediated by the complement cascade protein C1q. The complement cascade functions in innate immunity by recognizing and clearing pathogens through phagocytosis and pathogen membrane disruption. In the developing brain, synaptic pruning of excess or weak synapses is critical for proper neuronal connectivity and complement cascade protein C1q has been shown to trigger synapse elimination via engulfment by microglia, the resident macrophages of the central nervous system [164,165]. Interestingly, macrophages also play an important role in limb regeneration in salamanders [166].

Why might immune function be frequently repurposed for development? I propose two reasons. First, the logic of immunity, which targets suppression based on information about the target (i.e, self vs non-self), can be inherently useful for targeted suppression of gene expression or cell-type. For similar reasons, and as others have pointed out [167], humans have also found repurposing immune systems extremely useful for biotechnology (CRISPR, restriction enzymes, RNAi, CAR-T cells). A second reason that immune systems may be frequently repurposed is based on an evolvability argument. It seems reasonable that, from a fitness perspective, pathogens are a (the?) primary challenge for living organisms. For this reason, albeit rather speculatively, I propose that evolution of immune or defense systems would be a primary requirement and that developmental refinement of form would be a secondary target for natural selection during early evolution.

example of the fourth mode of adaptation enabled by genetic conflict with TEs.

2.4.2. Detection and silencing of transposable elements by piRNAs in Drosophila

As their name indicates, the essential nature of transposable elements is that they move and this mobility is their Achilles heel. The current working model for how mobile elements are detected in *Drosophila* is that their movement will inevitably cause them to land in a genomic region designated a piRNA cluster [99]. Once inserted into a piwi-interacting RNA (piRNA) cluster, assuming the insertion does not inactivate the cluster by disrupting cluster regulatory sequences, the TE insertion is transcribed and processed into piRNA. Recognition of a harmful TE family through its insertion into a piRNA cluster represents the ultimate detection phase, based on its mobility. piRNAs are 23–30 nt RNAs that are in complex with a class of Argonaute proteins designated Piwi proteins, which form a distinct clade of Argonautes present across Metazoa. piRNAs, in complex with Piwi proteins, have a central function in TE silencing across Metazoa and their biogenesis and function have been the subject of several excellent recent reviews [87–91]. In *Drosophila* they are best known for their capacity to target TE sequences for silencing with anti-sense piRNAs targeting TE mRNAs through their sequence complementarity. Silencing is mediated post-transcriptionally, primarily by the slicer activity of the Piwi protein Aubergine, and within the nucleus, by Piwi that can trigger silencing through heterochromatin formation at TE insertions.

2.4.3. Co-option of piRNA mediated defense for gene regulation

As a mechanism of genome defense, piRNA silencing has properties that make it a useful tool for host tinkering. In particular, it can recognize certain sequences and execute a number of biochemical functions on these sequences. For example, both in silkworm and nematodes, piRNA silencing plays a role in sex determination beyond the ancestral TE silencing function. In *C. elegans,* most piRNAs do not directly target transposons. Instead, it appears that piRNA mediated genome defense in *C. elegans* is mediated through a modified mechanism [100–102]. Foreign DNA of any kind, including transgenes, can be recognized by a profile of piRNAs that appear to be random sequences. Since these piRNAs have the capacity to target both foreign and endogenous genes, how are endogenous genes protected? The current model is that a second class of RNA provides protection on the part of endogenous genes. In the absence of this protection, foreign or TE transcripts are ultimately recognized and become the target of piRNA silencing.

piRNA mediated gene regulation plays an important role in *C. elegans* sex determination and dosage compensation [103]. *C. elegans* males have a single X chromosome whereas hermaphrodites have two. In hermaphrodites, a 1:1 X-to-autosome ratio leads to inactivation of master sex determination factor *xol-1*, allowing for proper sex-chromosome dosage compensation in females. In males, a 1:2 X-to-autosome ratio results in increased expression of *xol-1* and, in turn, proper male development. How does the dose of X chromosomes regulate sex determination? A number of factors designated X signal elements (XSEs) act cooperatively in XX hermaphrodites to suppress *xol-1* [104,105] and the most highly expressed piRNA encoded on the X chromosome functions as a suppressor of *xol-1*. This piRNA, designated *21ux-1*, targets *xol-1* for repression in hermaphrodites, allowing for robust hermaphrodite function [103]. In a striking example of convergent evolution in Lepidoptera, a piRNA derived from the W chromosome is also critical for sex determination in ZW silkworm females[106]. This W-linked piRNA targets the Z-linked transcript *Masc* for degradation. This remarkable convergence reveals piRNA-mediated suppression as a versatile mechanism for enabling regulation across sex chromosomes.

piRNAs have also proven to regulate endogenous gene expression in mammals. In male mice, piRNAs have been partitioned into three classes based on the timing of their expression in the germline relative to meiosis - prenatal, pre-pachytene and pachytene piRNAs [107]. Prenatal and pre-pachytene piRNAs contain abundant TE sequences and are involved in TE silencing prior to the pachytene stage of meiosis. On the other hand, pachytene piRNAs, which become expressed in the male germline during meiotic pachytene and are the most abundant piRNA in adult mouse testes, are largely derived from long intergenic non-coding transcripts that lack TE sequences. Since they lack TE sequences, the function of pachytene piRNAs is not well understood. However, studies indicate that the TE silencing function of piRNAs may have been co-opted for male fertility through the regulation and directed cleavage of germline mRNAs [108–112]. This function has been revealed by genetic analysis of two different pachytene piRNA clusters. A promoter deletion of the *pi6* piRNA cluster leads to defective spermatogenesis, coincident with misexpression of several mRNAs that are normally cleaved by piRNAs derived from the *pi6* cluster. A second piRNA cluster (*pi18)* regulates an additional gene essential for spermatogenesis, presumably through a similar mechanism [113].

Across animals, 3′ UTRs are a source of piRNAs that also have poorly understood function [114,115]. In mammals and birds, these piRNAs are associated with transcripts carrying TE sequences and are likely involved in TE silencing [115]. However, in flies, 3′ UTR based piRNA biogenesis may have been recruited directly for gene regulation, independent of TE silencing. *Traffic jam* is a gene expressed in the somatic tissue of the ovary and is a large source of 3′ UTR piRNAs with an apparent role in regulating a second gene, *FasIII* [116]. Rather than being triggered by a TE within the 3′ UTR, piRNA biogenesis is instead driven by a *cis* element in the UTR that folds into a hairpin designated a T-hairpin structure [117,118]. A second example of 3′ UTR piRNA biogenesis reveals a mode of gene regulation not by piRNA targeting, but by direct Piwi-mediated mRNA destabilization. In the case of *Drosophila* c-Fos, Piwi destabilizes the mRNA transcript and triggers the production of piRNA from the 3′ UTR[119]. These piRNAs are apparently non-functional and the production of piRNAs is simply a readout of direct Piwi-dependent transcript degradation of c-Fos

3. Mixed modes of conflict enabled adaptation

In describing these four modes of adaptation driven by TE-host conflict, I made an implicit assumption of independence across modes. For example, for adaptation by co-option of TE encoded *cis*-regulatory sequences (Mode 1), I described regulation independent of host defense mechanisms. Likewise, for gene regulation by host defense (Mode 4), the examples provided (sex-determination by piRNA in nematodes and butterflies and piRNA regulation of spermatogenesis genes in mice and oogenesis genes in flies), the piRNA sequences themselves did not correspond to TE sequences (though it should be noted that divergence from original TE sequences might make this difficult to confirm). However, in reality, there is crosstalk between these four modes of adaptation. In particular, it appears that host defense mechanisms themselves might play an important role in adaptation through modes 1, 2 and 3. Here I provide several examples of how adaptation from TE sequences might be capacitated by host systems of genomic immunity.

3.1. PEG10

Paternally Expressed 10 (*PEG10*) is an imprinted gene in mammals and is only expressed from the paternally inherited allele [120]. It was derived from a Ty3-like retrotransposon and represents an example of Mode 2 of TE driven adaptation. Like related Ty3 retrotransposons, *PEG10* has maintained the capacity to encode two different ORFs (Gag and Gag-Pol fusion) via frameshifting [121]. The precise function of PEG10 is poorly understood, but a paternal copy is necessary for proper placental development [122,123]. A recent CRISPR screen [124] revealed that *ATF7IP* has an important role in regulating the silencing of *PEG10*. Incidently, *ATF7IP* also targets TEs for H3K9me3 deposition [125] and stabilizes the histone methyltransferase SETDB1, enabling heterochromatin formation via the HUSH complex. In light of the critical roles that H3K9me3 and the HUSH complex have in protecting the genome from TEs, this suggests that essential functions of *PEG10* are regulated by mechanisms that also target TE silencing. In fact, tight control of *PEG10* is critical and its misregulation has been associated with Amyotrophic Lateral Sclerosis (ALS) [126]. For these reasons, the endogenous function of *PEG10* appears to have been facilitated by host TE defense mechanisms that lead to imprinting and proper regulation.

3.2. KRAB zinc-finger proteins

A second way in which modes of TE driven adaptation are driven simultaneously by overlapping modes is represented by the evolution of Krüppel associated box (KRAB) zinc-finger proteins. KRAB zinc-finger proteins evolved in the ancestor of lobe-finned fish and tetrapods and are highly abundant in mammalian genomes, with copy number in the hundreds [98,127]. KRAB domains are strong transcriptional repressors and, when coupled to a DNA binding domain, can trigger gene silencing [67]. Along with high copy number, KRAB zinc-finger proteins have zinc-finger arrays that range from low single digits to dozens [128]. Since zinc-fingers determine the sequence of the DNA bound by KRAB zinc-finger proteins, these highly variable zinc-finger array lengths can target a variety of different DNA sequences. What has driven the diversification of KRAB zinc-finger proteins? It is now clear that many of these repressor proteins directly target DNA sequences within TEs leading to their silencing [129]. Moreover, this diversification was likely driven by an evolutionary arms race with TEs that evolve new sequences that render them no longer targets for KRAB zinc-finger repression [97]. However, one outcome of this arms race is that genes as well as TEs have become targets of KRAB zinc-finger repression through nearby TE remnants [130]. For example, the *Bglap3* gene is silenced in the liver of adult mice by KRAB zinc-finger *ZFP932* through an internal LTR element known as an IAP element, representing a Mode 1 form of adaptation overlapping with adaptation through recruitment of a silencing pathway.

3.3. Drosophila telomeres

As previously discussed, *Drosophila* telomeres represent a mode TE-host conflict adaptation not by a single TE insertion, but rather through the active proliferation of multiple TE lineages (Mode 3). However, this proliferation is not unconstrained. Rather, regulation by piRNA silencing plays a critical role in this example of TE domestication. The working model for telomere maintenance in *Drosophila* proposes that telomere length homeostasis is maintained by a balance of piRNAs that regulate the transposition of telomeric retrotransposons *TART, Het-A* and *TAHRE* [131]. These three elements are the target of piRNA silencing and telomeric arrays containing these elements function as piRNA clusters [132,133]. Disruptions in piRNA silencing lead to increased expression of telomeric retrotransposons [134] and an increased number of telomeric fusions that appear to arise from loss of the capping proteins at the ends of the retrotransposon array [135]. Additionally, disruptions in piRNA silencing lead to increased transposition of telomeric retrotransposons into broken chromosome ends [136]. Overall, it appears that adaptation to protect *Drosophila* chromosome ends via retrotransposons has been enabled by piRNA-mediated genome defense to keep the telomeric retrotransposons in check.

3.4. Regulation of mRNA

In addition to slicing or silencing TE RNAs, piRNAs also have a role in regulation of endogenous mRNA stability, translation and decay. This has been observed in both mice and flies. In a striking parallel across hundreds of millions of years of divergence, germline mRNAs are both positively and negatively regulated through piRNA mechanisms. In mice, as previously mentioned, piRNAs in the male germline play a role in developmental mRNA elimination [110,111]. In *Drosophila* embryogenesis, mRNA decay of maternal transcripts is also facilitated by piRNAs that target 3′ UTR sequences [137]. Similar mechanisms also occur within germline stem cells [138,139]. Strikingly, in a different developmental context, piRNAs in both mice and flies can promote translation. In flies, the Piwi protein Aubergine promotes stabilization and germline translation for mRNAs with 3′ UTR piRNA targets [140–142]. Likewise, in mice, the PIWI protein known as MIWI targets a subset of mRNAs during spermatogenesis via piRNAs with a partial 3′ UTR match and enhances translation by recruiting members of a larger complex [143]. At least in *Drosophila*, this mode of mRNA regulation of the *nanos* transcript - both de-adenylation in the embryo and translation activation in the germline - is enhanced by piRNAs that correspond to TE sequences [144]. Thus, this represents a case of combined modes of adaptation through TE-host conflict, where piRNAs targeting TE sequences enable gene regulation through the piRNA mediated genome defense machinery.

3.5. Sex determination in melon

A final example of a combined mode of adaptation is provided in melon. Plants can adopt a number of reproductive strategies, ranging from those with perfect bisexual flowers to those with separate sexes (dioecy). In melons, a transposon insertion can change plant reproductive mode from monoecious (a plant with distinct male and female flowers) to gynoecious (a plant with only female flowers) [145]. This occurs through a TE insertion that turns off the gene *CmWIP1*, a zinc-finger transcription factor that enables the male program in developing flowers. Interestingly, the TE insertion does not directly cause a mutation in *CmWIP1*. Rather, the TE insertion triggers methylation of the *CmWIP1* promoter, reducing its expression and turning off the male developmental program. Since DNA methylation in plants silences TEs as a mechanism of genome defense, the DNA methylation coupled with a TE insertion represents a mode of sex determination through gene regulation that arises from a joint mode of adaptation driven by host-TE conflict.

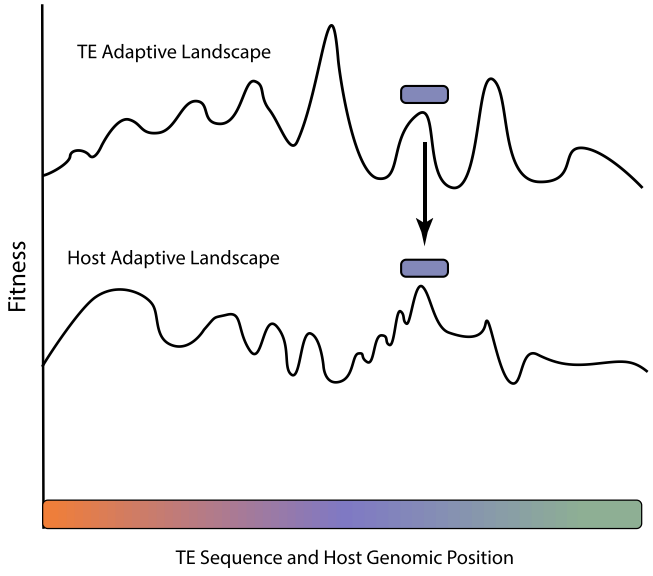
4. Information exchange between replicators on different adaptive landscapes: Final thoughts on adaptation enabled by TE-host conflict

Based on the examples provided here, we can see that diverse modes of adaptation are enabled by genetic conflict between TEs and hosts. These modes of adaptation are somewhat peculiar, because they arise from the interaction of tightly coupled but *distinct* replicating lineages: a lineage of replicating TEs within a lineage of replicating hosts. In the case of TE co-option, adaptation within a replicating TE lineage becomes beneficial to another distinctly replicating host lineage on a different adaptive landscape (See Box 3).

The mutations provided by TE insertions are very unique. Unlike errors that arise during DNA replication, TE insertions have high information content imbued by prior natural selection on that replicating lineage. For TEs that recently invaded through horizontal transfer, the selective regime shaping adaptation on the TE lineage will have occurred *outside* of the host. For TEs that are long time genome residents of a host genome, they are also shaped by selection *inside* the host genomic ecosystem, to recruit host machinery for proliferation and avoid genome defense. These differences in the history of selection are likely to influence the chance a new TE insertion will be selected through a fitness benefit conferred on the host.

Since TE insertional mutations have high information content shaped by natural selection, one might question whether these types of mutations are consistent with the general view of evolution described as the Modern Synthesis. The Modern Synthesis arose in the first half of the 20th century and integrated the Darwinian theory of evolution with Mendelian genetics. The central tenets of the Modern Synthesis are that mutations arise randomly and that evolution proceeds by changes in allele frequency through the act of natural selection. The Modern Synthesis relies on the assumption that mutations are random with respect to future adaptive potential. Are TE insertional mutations random in this sense? Since resident TE sequences contain information about the genome ecosystem in which they reside, one might suggest that the mutations they induce are not "random" with respect to host fitness. Instead, their history of natural selection may shape them to cause mutations on average more beneficial than those, for example, caused by replication errors. Unfortunately, the word "random" is often confused with the concept of something being *uniformly* random, with all fitness effects *equally* likely. However, even a system of mutation skewed away from deleterious effects is still random, just as the process for rolling two ones on a pair of dice, though unlikely, is also random. For this reason, even if TE insertions are more likely to be beneficial compared to other types of mutation, adaptation of the kind discussed here would not contradict the Modern Synthesis. The only type of mutation that would challenge the Modern Synthesis would be environment dependent

Box 3
TE co-option as information exchange between replicators on different adaptive landscapes.



Box 3 TE evolution is guided by the TE adaptive landscape, which includes the underlying TE sequence and the location/position within the respective genome. A corresponding adaptive landscape exists for the host. In places where the adaptive peaks are coincident, a TE insertion with a given sequence and location is jointly beneficial for the TE and host. Information within the TE imbued by prior natural selection on the TE can therefore provide host benefit.

mutation that increases that chance of beneficial mutations *specifically in the environment where the same mutations would be more beneficial* (for a discussion of these matters, see [146–148]). To the best of my knowledge, this has yet to be formally demonstrated for TE insertions. Nonetheless, how genetic conflict arising from meiosis and the release of parallel natural selection on hosts, and lineages within hosts, act as a forge of innovation is worth noting when we seek to explain the diversification of eukaryotic life.

TEs evolve under a selective regime that favors their proliferation but this can enable the evolution of sequences also suitable for the host. In this case, there may be an "allegiance switch", whereby information is transferred from a replicator on an adaptive landscape for TE proliferation to a host replicator residing on a different adaptive landscape. This is expected to occur in locations on the two adaptive landscapes where adaptive peaks are coincident with respect to the underlying sequence and genomic position. This would correspond to a location where a sequence that enhances TE function can also enhance host function (Box 3). In this sense, the informational content of a new mutation (i.e, a new TE insertion) is shaped by the history of previous selection experienced by the TE lineage on its own adaptive landscape. This represents a form of adaptation on the part of the host that is distinct from replication errors, which lack a previous history of natural selection acting on the new mutant sequence.

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Declaration of Competing Interest

None

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