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A Field Guide to Eukaryotic Transposable Elements

Jonathan N. Wells and Cédric Feschotte

Department of Molecular Biology and Genetics, Cornell University, Ithaca, New York 14850; email: jnw72@cornell.edu, cf458@cornell.edu

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Abstract

Transposable elements (TEs) are mobile DNA sequences that propagate within genomes. Through diverse invasion strategies, TEs have come to occupy a substantial fraction of nearly all eukaryotic genomes, and they represent a major source of genetic variation and novelty. Here we review the defining features of each major group of eukaryotic TEs and explore their evolutionary origins and relationships. We discuss how the unique biology of different TEs influences their propagation and distribution within and across genomes. Environmental and genetic factors acting at the level of the host species further modulate the activity, diversification, and fate of TEs, producing the dramatic variation in TE content observed across eukaryotes. We argue that cataloging TE diversity and dissecting the idiosyncratic behavior of individual elements are crucial to expanding our comprehension of their impact on the biology of genomes and the evolution of species.

INTRODUCTION

Transposable elements (TEs) are mobile DNA sequences capable of replicating themselves within genomes independently of the host cell DNA. They typically range in length from 100 to 10,000 bp, but are sometimes far larger (6). Along with viruses, TEs are the most intricate selfish genetic elements. They frequently encode proteins with multiple biochemical activities as well as complex noncoding regulatory sequences that promote their transposition.

The boundary between TEs and other invasive genetic elements such as viruses is fluid. Here we define a TE as a genetic element capable of chromosomal and replicative mobilization in the germline, thereby increasing in frequency through vertical inheritance. This definition incorporates nonautonomous elements such as short interspersed nuclear elements (SINEs) and miniature inverted-repeat transposable elements (MITEs). It also includes endogenous retroviruses (ERVs) but excludes endogenous elements originating from viruses that do not integrate and mobilize in the host germline (47). While the capacity for vertical inheritance through the germline is a defining feature of all TEs, it should be noted that horizontal transfer of TEs between species also occurs and is an important factor in their long-term success (60).

All eukaryotic genomes examined thus far, with a few notable exceptions (see the section titled Transposable Element Abundance and Genome Size), are known to harbor TEs. Across most organisms, TE content correlates strongly with genome size, and in some species it constitutes as much as 85% of the genome (160) with host protein-coding regions resembling little more than islands in a sea of TEs (44). However, the fraction of the genome occupied by TEs does not correlate with organismal complexity: both complex multicellular organisms, such as conifers (119) and salamanders (118), as well as single-celled organisms, such as *Trichomonas vaginalis* (21) and *Amncaliia algerae* (123), may contain prominent TE fractions. Thus, TEs are an omnipresent feature of eukaryotic genomes.

In the decades since Barbara McClintock's (111) far-seeing ideas on controlling elements, the profound effect that TEs have had on eukaryotic evolution has become clear. In everything from the size and structure of genomes to the proteins they encode and the regulation of such, TEs play a critical role (1, 10, 13, 25, 27, 44, 49, 137). If we wish to understand how TEs have impacted the diversification and biology of species, we must therefore begin with an understanding of the diversity and biology of TEs themselves. In this review, we first provide an overview of the classification of eukaryotic TEs and a brief examination of their evolutionary origins and relationships. Next, we look at the variation of TE content across species, highlighting the extremes in abundance and diversity. We close with a discussion of the forces underlying such variation, focusing on factors intrinsic to the TEs themselves.

CLASSIFICATION OF EUKARYOTIC TRANSPOSABLE ELEMENTS

The most fundamental division of eukaryotic TEs, introduced by David Finnegan (51) in 1989, distinguishes two major classes based on their transposition intermediates: class I—retrotransposons, and class II—DNA transposons. Class I elements replicate via an RNA intermediate, which is then reverse-transcribed back into a DNA copy and integrated into the genome. Because the original template element remains intact, retrotransposons are commonly referred to as copy-and-paste elements. In contrast, the majority of (but not all) class II elements mobilize through a cut-and-paste mechanism, in which the transposon itself is excised and moved to a new genomic location. Both classes can be further subdivided many times, first into subclasses (or orders) (162), which are primarily delineated according to their mechanisms of replication and/or chromosomal integration (**Figure 1**), and then into superfamilies and families, which are more accurately characterized in terms of phylogenetic relationships (4, 35, 49, 162, 169).

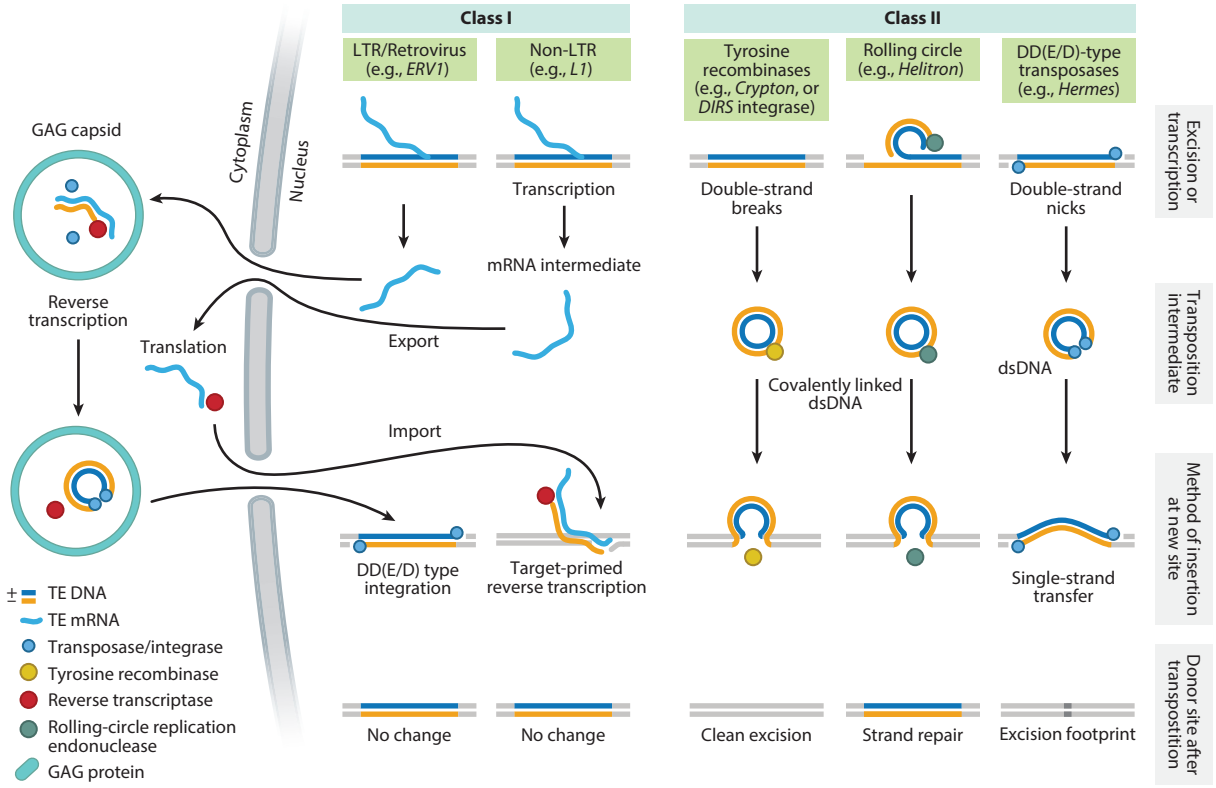


Figure 1

Summary of replication mechanisms and transposition intermediates, including proposed transposition intermediates and key replication steps for five TE subclasses. YR retrotransposons and *Maverick/Polintons* are not shown, but the former are expected to transpose via the same intermediate as class II YR transposons (i.e., *Cryptons*). The mechanism of *Mavericks/Polintons* has not yet been studied, but based on the presence of protein-primed type B DNA polymerase, they are expected to transpose by direct synthesis of a DNA copy (78). For comprehensive reviews on transposition mechanisms, readers are referred to References 28 and 68. Abbreviations: dsDNA, double-stranded DNA; LTR, long terminal repeat; mRNA, messenger RNA; TE, transposable element; YR, tyrosine recombinase.

In practice, TE families are usually defined using the 80–80–80 rule, which specifies that insertions are members of the same family if they are longer than 80 bp and share at least 80% sequence identity over 80% of their length (162). These families can then be represented by their majority-rule consensus sequence, as constructed from sequence alignments of multiple copies. In principle, the consensus sequence of a TE family represents an approximation of the ancestral TE that seeded the family (76, 143). This is particularly accurate if the family has expanded rapidly in a single burst of activity and each copy has evolved neutrally thereafter. There are many cases where these assumptions are violated, however, and as such, the 80–80–80 rule and corresponding consensus sequences do not always reflect the true phylogenetic structure of TE families. *L1* elements in mammals, for example, produce distinctive ladder-like phylogenies that require more careful analyses before they can be defined as families or subfamilies (82, 143).

TEs can also be classified according to whether or not they are able to move autonomously. Autonomous elements are those that encode the enzymatic machinery necessary for their own transposition. Nonautonomous elements are typically noncoding but still capable of mobilization

in *trans* by hijacking the machinery produced by their autonomous counterparts. Families entirely composed of nonautonomous elements often emerge as parasites of other TEs. Some of these originate from deletion derivatives of autonomous elements, as is the case for most MITEs, which comprise only the terminal inverted repeats (TIRs)—and thus transposase binding sites—of ancestral, autonomous DNA transposons (50, 168). But others emerge de novo from non-TE sequences. For instance, SINEs are usually derived from noncoding genes such as transfer RNAs (tRNAs), transcribed by RNA polymerase (Pol) III and *trans*-mobilized by the machinery of long interspersed nuclear elements (LINEs) (31, 120). However, most SINEs are not merely retrogenes but have acquired composite sequences promoting LINE parasitism and amplification (reviewed in 31, 120) (see the section titled Chimeric Elements and Modular Evolution).

Class I Retrotransposons

Retrotransposons can be divided into three major subclasses according to their mechanism of replication and integration: (*a*) long terminal repeat (LTR) elements [mobilized by an integrase (IN)], (*b*) target-primed non-LTR elements, and (*c*) tyrosine recombinase (YR)-mobilized elements. Of these, non-LTR elements are the simplest structurally and usually contain two coding open reading frames (ORF1 and ORF2). The function of ORF1 protein remains poorly understood, and it is dispensable or absent in some groups of non-LTR elements [it is absent in *R2*, for example (17)]. When they are required, as in *L1* elements, ORF1 proteins form an oligomeric product involved in the recognition and transport of the template RNA to the nucleus (137). ORF2 protein has both endonuclease and reverse transcriptase (RT) activities, the latter of which is essential for target-primed reverse transcription (TPRT) (104, 114, 137). In *L1*, this process initiates with the formation of a single-stranded nick by the endonuclease, usually at a 5′-TT/AAAA-3′ site, followed by hybridization of the host DNA with the 3′ end of the RNA template, reverse transcription, and finally integration of the newly synthesized complementary DNA (cDNA) strand (137) (**Figure 1**). A hallmark of this process is that the reverse transcription step frequently terminates early, leading to 5′ truncation of the copy. Because non-LTR elements are expressed from an internal Pol II promoter located in their 5′ termini, such truncation generally prevents further propagation of the newly inserted copy (137) (**Figure 1**).

The structures, coding capacity, and replication mechanisms of LTR elements are more complex and closely resemble those of retroviruses, to which they are evolutionarily related (35). Autonomous LTR elements contain a minimal set of two distinct genes (*gag* and *pol*), generally expressed as a single polycistronic RNA transcribed from a Pol II promoter located within the LTR itself. Both *gag* and *pol* encode polyproteins that are posttranslationally cleaved by a *pol*-encoded protease (PR). *Pol* also encodes RT, Ribonuclease H (RNase H), and IN activities. Reverse transcription uses a tRNA primer and occurs on a genomic RNA template encapsidated within a cytoplasmic viral-like particle assembled from *gag*-encoded proteins (for further details, see 163). The cDNA product is bound by the IN protein, which mediates nuclear localization and integration into the host chromosome through a process similar to that of cut-and-paste transposases (28, 68). Indeed, the catalytic domain of IN belongs to the DDE nuclease family (see the section titled Chimeric Elements and Modular Evolution).

The process of retroviral replication and integration is essentially the same as that of LTR elements, and the only substantive difference arises from the acquisition of fusogenic *env* genes by retroviruses (35). *Env* genes are often lost, and consequently retroviruses that are active in the germline [e.g., koala retrovirus (102)] frequently become endogenized (108). A classic example of this is *IAP*, of which only a single remaining copy in the C57BL/6 mouse genome still produces a functional retrovirus (136).

YR retrotransposons represent a third major subclass of class I elements, but they are relatively understudied (28). They are most similar to LTR elements in their genetic structure, but differ notably by encoding YR in place of IN. YR elements possess terminal repeat sequences, but the structure of these varies between the major superfamilies of YR retroelements: For example, *DIRS* elements have inverted repeats, but these are nonidentical, in contrast to true LTRs, whereas *Ngaro*, *VIPER*, and *TATE* elements appear to have direct repeats laid out in a split-repeat pattern (61, 135). The function of the terminal repeats and mode of replication of YR elements remain poorly characterized, but a proposed mechanism for *DIRS* involves reverse transcription of the messenger RNA template, circularization of the single-stranded cDNA copy (initiated by the pairing of the terminal repeats), synthesis of the second cDNA strand, and finally chromosomal integration mediated by YR (19, 127).

We must make a brief mention of *Penelope* elements. These curious TEs were first discovered as mutagenic agents in *Drosophila virilis* in 1997 but for some time remained the only known representatives of their class (43). Two features of *Penelope*-like elements stand out: first, the presence of pseudo-LTRs and second, a GIY-YIG (amino acid motif) endonuclease domain, which is not shared with any other retroelement subclasses (42). Based on their likely reliance on TPRT for transposition, they may be classified as non-LTR elements, but phylogenetic analyses of their RT domain suggest that they define a distinct monophyletic group. This group is equally distant from LTR and non-LTR elements and is most closely related to telomerase, implying that these elements diverged early in eukaryotic evolution (5, 42). Consequently, *Penelope*-like elements may be considered a separate subclass of retroelements, which turns out to be relatively common in animals (4).

Class II DNA Transposons

At present, we know of four major groups of DNA transposons: (*a*) cut-and-paste elements mobilized by DDE transposases [named after their signature triad of aspartic and glutamic acid catalytic residues—DD(E/D)] (32, 169) or (*b*) by YR (called *Cryptons*) (89), (*c*) rolling-circle elements [also known as *Helitrons* (77, 153)], and (*d*) the most enigmatic—self-synthesizing transposons, known as *Mavericks* or *Polintons* (48, 78, 130). Of these, DDE transposons and *Cryptons* are the simplest, typically consisting of a single ORF encoding a recombinase flanked by short TIRs. As such, these elements resemble bacterial and archaeal insertion sequences in their structure (142). While *Cryptons* are relatively rare in eukaryotes (89), DDE transposons are the most diverse and widespread of all TEs, with at least 17 large superfamilies defined by phylogenetically distinct transposases (4, 8, 49, 169). In fact, the success of this subclass is such that the DDE transposase is a contender for the oldest and most abundant gene on earth (7).

The precise mechanism of DDE transposition varies between superfamilies, but for all eukaryotic members thus far examined, the process is initiated by transposase-catalyzed nucleophilic attack of a water molecule in close proximity to the ends of each TIR, eventually resulting in direct excision and relocation of the transposon DNA (68). While the process itself is nonreplicative, these elements can still increase in copy number to form abundant families in the genome. One amplification strategy involves preferential transposition during host DNA synthesis from replicated to unreplicated sites, effectively causing the transposon to be replicated twice (58, 138, 145). Cut-and-paste transposons can also be duplicated when the double-strand break left behind at their excision site is repaired via homologous recombination. During this process, abortive repair, strand slippage, and template switching commonly lead to the formation of internally deleted transposon copies (40, 70, 139). While these nonautonomous elements often lose their coding capacity, they may retain the binding site recognized by autonomous transposons. These short

elements often proliferate more effectively and at the expense of their autonomous counterparts, forming extensive families of MITEs (50, 115, 168).

Helitrons are abundant in many eukaryotic lineages, including in model organisms such as *Drosophila melanogaster*, *Caenorhabditis elegans*, and *Arabidopsis thaliana*, but remained uncharacterized until the early 2000s (77, 153). This was in part because they are mostly represented by nonautonomous elements that lack TIRs and other features of canonical DNA transposons. The identification of the first autonomous *Helitrons* in various species, which code for a large Rep/Hel protein comprising an HUH endonuclease domain (i.e., Rep—replication initiator) fused to a helicase (i.e., Hel), led to the realization that they must use a fundamentally different mobilization mechanism than that of cut-and-paste elements (77).

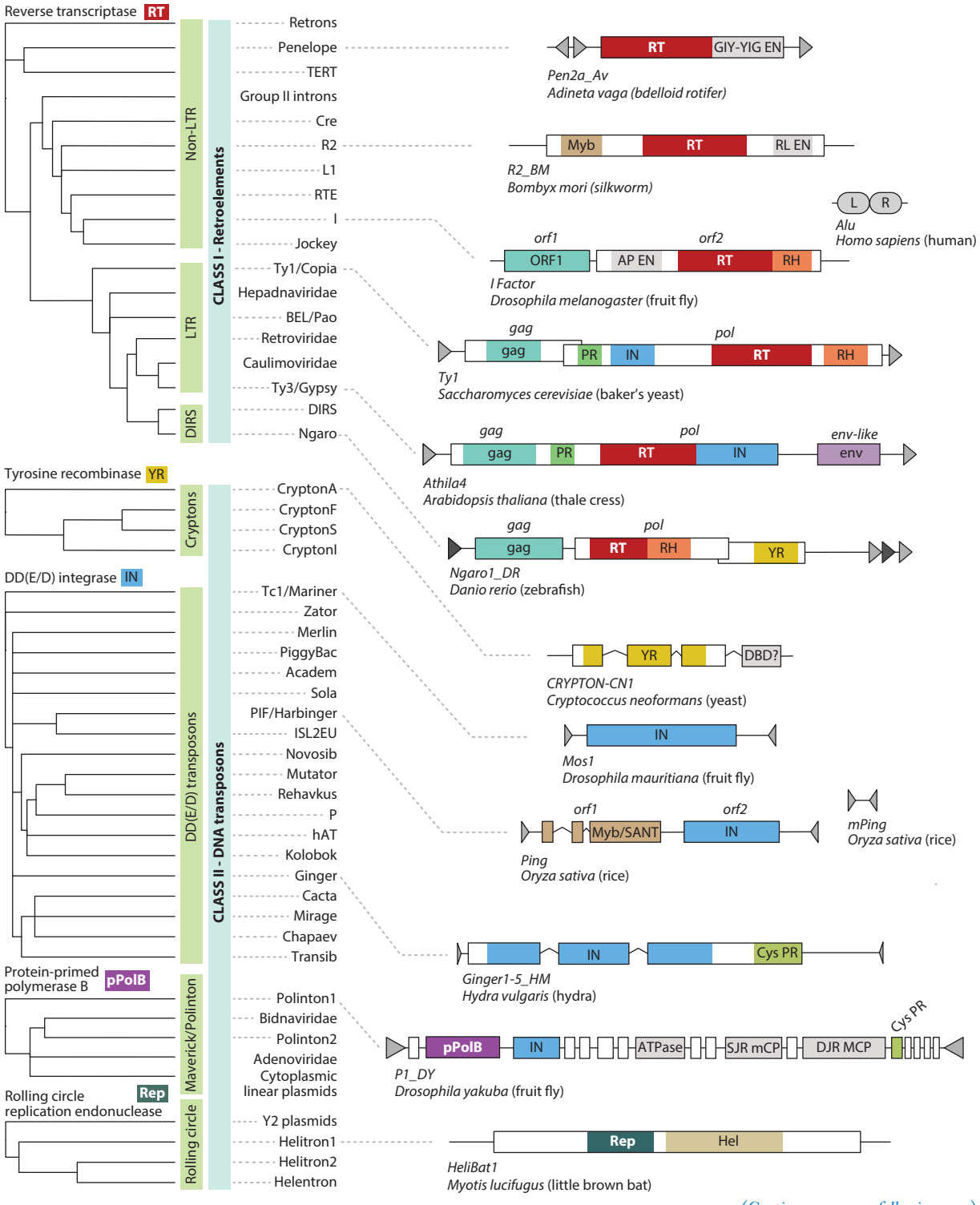
Significant insights into the *Helitron* transposition mechanism were recently gained through the study of *Helraiser*, an active autonomous element resurrected from inactive *HeliBat1* elements in the *Myotis lucifugus* genome (63, 128) (**Figure 2**). Functional studies of *Helraiser* suggest a peel-and-paste mechanism in which a covalently linked circular double-stranded DNA (dsDNA) intermediate is formed by peeling off the sense strand and (probably) synthesizing the second strand as the circle rolls towards the 3′ end of the *Helitron* (62) (**Figure 1**). However, while *Helraiser* transposes replicatively, genetic data from maize suggest that some *Helitrons* are able to directly excise rather than copy, indicating that there is still work to be done to elucidate the mechanisms of *Helitron* transposition (100).

Mavericks (or *Polintons*) are yet another poorly characterized class of DNA elements, which are exceptional for their size (15–20 kb) and complexity, consisting of up to twenty protein-coding genes flanked by long, 400–700-bp TIRs (48, 78, 130). These elements are widespread in eukaryotes, but they are generally present in low copy number (dozens per genome), with a few known exceptions, such as in the protist *T. vaginalis*, where they have exploded to occupy one-third of the genome (130). *Mavericks/Polintons* share similarities to disparate groups of dsDNA viruses (78, 91, 130, 170). This includes a protein-primed type B DNA polymerase (pPolB) most closely related to that of adenovirus, which suggests that they replicate via direct synthesis of a DNA copy [hence the proposed name self-synthesizing transposons (78)]. They also encode a DDE integrase most closely related to retroviral IN, which is consistent with the fact that, like most retroviruses, they create 5- or 6-bp target site duplications upon chromosomal integration (48, 78, 130).

Many *Maverick/Polinton* elements are also predicted to encode double and single jelly roll capsid-like proteins (91, 94). This observation, along with their relationship to viruses and, in particular, the Mavirus virophage, has led to the proposal that they may represent endogenous viruses or virophages (53, 94). Lending support to this idea is the recent discovery of abundant *Polinton*-like viral entities in freshwater lake habitats (11). The connection with virophages—satellite elements that parasitize much larger dsDNA viruses—is particularly intriguing, as it suggests that the integration and endogenization of *Maverick/Polinton* elements into the genome of eukaryotic organisms might confer protection against some of these giant viruses (52).

EVOLUTIONARY ORIGINS OF EUKARYOTIC TRANSPOSABLE ELEMENTS

When and how did the major groups of TEs described above originate, and how do they relate to each other? The best way to address these questions is through a phylogenomic framework, which integrates the taxonomic distribution of the elements with phylogenetic analyses of their shared core proteins (4, 162, 167, 169). This approach has gained power with the increasing diversity of host genome sequencing projects and the development of powerful tools to automate the annotation of TEs (2, 55, 121). However, it also has limitations. TE sequences tend to evolve rapidly, and



(Caption appears on following page)

Figure 2 (*Figure appears on preceding page*)

Structure and taxonomy of eukaryotic transposable elements. The left panel lists unrooted cladograms showing putative relationships between the major TE superfamilies, based on phylogenies of core protein domains for five subclasses (4, 35, 67, 89, 96, 169). The right panel depicts genetic structures of representative elements from each subclass. Outlined boxes are ORFs, shaded regions are defining protein domains, kinked lines are introns, triangles are repeated sequences, and rounded boxes (i.e., for Alu) are RNA elements. Domains with the same colors (except *gray*) indicate shared ancestry. Element lengths are not to scale. Abbreviations: AP, apurinic/apyrimidinic; DBD, DNA binding domain; DJR MCP, double jelly-roll major capsid protein; EN, endonuclease; Hel, helicase; IN, integrase; LTR, long terminal repeat; ORF, open reading frame; pPolB, protein-primed type B DNA polymerase; PR, *pol*-encoded protease; Rep, replication initiator; RH, Ribonuclease H domain; RL, type II restriction-like; RT, reverse transcriptase; SJR mCP, single jelly-roll minor capsid protein; TE, transposable element; YR, tyrosine recombinase.

even the most common and constrained TE protein domains (such as RT or the DDE catalytic region) can be difficult to align with confidence, especially when considering elements from different superfamilies (4). In addition, most TEs have undergone numerous horizontal transfers at different points in their history, even between distantly related taxa [e.g., between vertebrates and invertebrates (60)]. Furthermore, entire TE lineages may be lost or go extinct during evolution (157). As a result, TE phylogenies often conflict with those of host species, making it difficult to trace the evolutionary history and origin of TEs.

These caveats aside, a number of important conclusions can be drawn from the observations gathered over the last few decades. First, all of the major subclasses of elements (**Figure 2**) are widely distributed across the eukaryotic tree, each being found in at least two of the nine or so currently defined supergroups (18). Second, phylogenetic topologies of the core TE proteins are consistent with the idea that each of these subclasses was already in existence early in eukaryotic evolution. Third, the evolution of TEs is highly modular, with recurrent gain and loss of proteins from a shared pool of conserved domains.

Deep Evolutionary Roots of Transposable Element Proteins

Despite the bewildering diversity in the structure of different elements, the number of distinct protein families involved in replication and transposition is surprisingly small, comprising roughly five defining catalytic domains (RT, DDE IN, YR, HUH/Rep, and pPolB) (**Figure 2**). Remarkably, despite their seemingly disparate mechanisms, HUH, RT, and pPolB domains all share a deeply conserved structural fold termed the RNA recognition motif (RRM), which is thought to have played an important role in the transition from the primordial RNA world (for a recent review, see 95). This fact, along with the widespread phylogenetic distribution of these proteins, indicates that the core enzymatic machinery of transposition—if not the TEs themselves—predates the emergence of eukaryotes (**Figure 2**).

Phylogenetic analyses of the main DDE transposase superfamilies are ambiguous, with many long branches and polytomies at the base of the tree (**Figure 2**). Nonetheless, at least six of the main DDE transposase superfamilies have been affiliated with those encoded by distinct groups of bacterial insertion sequences (IS): *Mutator* with IS256, Tc1/*mariner* with IS630, PIF/*Harbinger* with IS5, *Merlin* with IS1016, *piggyBac* with IS1380, and *Zator* with ISAz013 (8, 49, 88). These distant relationships should be treated with caution until they can be confirmed by structural alignments and mechanistic studies, but taken together they suggest that the divergence of some of these DNA transposon superfamilies predates the emergence of eukaryotes.

In contrast to DDE transposons, none of the remaining eukaryotic TE subclasses has unambiguous homologs in bacteria or archaea. While phylogenies point to a direct affiliation between bacterial, archaeal, and eukaryotic RTs [notably between that of group II introns and non-LTR

elements (23, 167, 173)], all extant eukaryotic retroelements are very distinct from their non-eukaryotic relatives.

In the case of rolling-circle replication elements, the HUH endonuclease involved in the transposition of *Helitrons* is also responsible for the mobilization of bacterial *IS91* transposons, but it appears likely that eukaryotic rolling-circle elements emerged independently of *IS91* elements, possibly from viruses or plasmids (67, 80). Similarly, although transposons mobilized by YR are common in bacteria and archaea, their enzymes do not phylogenetically cluster with those encoded by eukaryotic YR retrotransposons or class II *Cryptons* (61, 127, 135). Thus, most eukaryotic TE subclasses appear to have emerged shortly after the origin of eukaryotes.

Chimeric Elements and Modular Evolution

While phylogenomic analyses reveal the deep relationships between the core transposition enzymes that define the major TE subclasses, they offer limited insight into the origin of individual families and superfamilies (**Figure 2**). This is because TEs, together with other self-replicating elements like viruses and plasmids, form a densely connected evolutionary web characterized by the frequent exchange of protein-coding units. These exchanges involve both the core domains essential for transposition as well as accessory domains acquired from host genomes (4, 6, 91, 95), and they often blur the distinctions between TE classes and subclasses, and, for that matter, between TEs and other invasive elements. For example, while class I YR retrotransposons cluster together with LTR elements and retroviruses based on the phylogenies of their RT domains (**Figure 2**), phylogenies based on YR show them to be closely related to *Cryptons*—class II elements. Similarly, LTR retroelements, cut-and-paste DNA transposons, and *Mavericks/Polintons* all use a DDE recombinase for chromosomal integration. The sharing of these enzymes points to chimerism as a major force in the emergence and diversification of TEs (4, 6, 91, 95, 98, 127).

LTR retrotransposons are a fascinating example of this mosaic process. These elements appear to have evolved a unique transposition mechanism that borrows components from non-LTR elements and cut-and-paste DDE transposons (110). Because both non-LTR and DDE transposons appear to be evolutionarily older, LTR elements most likely arose by chimeric fusion between the two. One line of evidence supporting this scenario lies in the similarity between the RNase H domain (RH) of LTR and non-LTR elements. RH is another structural fold that arose near the origin of life, whose function is to degrade the RNA strand of DNA-RNA duplexes. Phylogenetic analysis of RH domains from LTR elements, non-LTR elements, and cellular genomes reveals that the LTR-derived RHs form a monophyletic group nested within the non-LTR clade (109). This tree is largely congruent with RT phylogenies, and by using host-derived RH sequences to root the tree, it can be inferred that non-LTR elements predate LTR elements. The ORF1 protein encoded by several non-LTR elements also bears sequence, positional, and functional (RNA-binding and chaperone activities) similarities to the LTR Gag protein, although some of these features may be the result of convergent evolution (29, 83, 84, 133). While the acquisition of other attributes such as tRNA-priming or the terminal repeats themselves remain mysterious, the data currently point to a model in which LTR elements emerged through fusion of a non-LTR retrotransposon with a DNA transposon. The latter provided the IN, while the former likely provided all the other protein domains.

SINEs also offer a compelling illustration of how highly successful TE families repeatedly emerge via chimeric assembly. Most SINEs are derived from Pol III-transcribed noncoding RNA, such as tRNA, 7SL, or 5S RNA, *trans*-mobilized by the machinery of LINEs (92). While some SINE families consist of little more than Pol III transcripts, many others have evolved complex mosaic structures that further enhance their transposition capacity. For instance, *Alu* elements

arose early in primate evolution by a process involving the fusion of two monomeric 7SL-derived SINEs that emerged earlier in the mammalian radiation (93). Since their appearance, *Alu*s have spawned many subfamilies and new composite elements that outnumber not only their monomeric progenitors but essentially all other TE families in primate genomes (10, 72). In the hominoid ancestor, a fusion between an *Alu*, a *VNTR* (variable number tandem repeat) and an LTR fragment gave rise to the *SVA* family (158). In the gibbon lineage, *SVA* in turn gave rise to another family of composite TEs called *LAVA*, which combines portions of *L1*, *Alu*, *VNTR*, and another *Alu* (20). *Alu*, *SVA*, and *LAVA* are all nonautonomous elements mobilized by the *L1* machinery, but *SVA* and *LAVA* have apparently acquired Pol II-driven promoters (65, 113, 132). Equally tortuous stories of SINE diversification via fusion and accretion of additional sequences have been described in plants and other animals (92).

VARIABLE SUCCESS OF TRANSPOSABLE ELEMENTS ACROSS SPECIES

Half a century has passed since the realization that the TE content of genomes varies greatly between species (15, 16). The characterization of ever more genomes has continued to expose this variation, but we still have only partial clues to the factors influencing TE accumulation and diversification across species. Some genomes contain just a few, if any TE families, while others are bloated with a bewildering diversity (**Figure 3**). Why? Answering this question is paramount to understanding the impact of TEs on genome evolution.

It has been proposed that the overall TE load of organisms across broad phylogenetic scales is dictated by effective population size, or *Ne* (106). This is because the efficiency of selection in removing deleterious mutations is proportional to *Ne*. This may explain, for instance, why TE insertions reach fixation more frequently in vertebrates than in fruit flies, which have relatively large *Ne*. But it cannot account for differences in TE abundance observed between species with comparable *Ne*, such as those within the same taxonomic order (79, 105, 124, 161) (**Figure 3**). Similarly, this theory offers little explanation as to why the diversity of TEs should be so variable between species or why certain TE types seem to be particularly successful in certain taxonomic groups. For instance, LTR elements are prevalent in flowering plants, while non-LTR elements dominate in mammals (117, 137) and DNA transposons prevail in zebrafish and *Caenorhabditis* nematodes (49). In the following section, we further illustrate such variation in TE abundance and diversity across species before discussing some of the factors that may be driving these phenomena (**Figure 3**).

Transposable Element Abundance and Genome Size

Thus far, very few eukaryotic species appear to lack TEs altogether. The best-known exceptions are apicomplexan protists such as *Plasmodium falciparum*, *Toxoplasma gondii*, *Encephalitozoon intestinalis*, and *Theileria parva*, which seem to have successfully purged TEs from their genomes (87). As a result, the latter two species now possess two of the smallest known genomes of any eukaryotes (26, 64). It is probably not coincidental that all these species are single-celled, obligate intracellular parasites and are predominantly asexual except for brief periods in their lifecycle—a feature which has been predicted to reduce TE load (9). Although the dearth of TEs in apicomplexans may be related to their peculiar lifestyle and reduced genomes, several other parasitic unicellular eukaryotes do harbor diverse and active TE communities (21, 103, 123, 129). For instance, *A. algerae* is an obligately intracellular microsporidian parasite with a tiny genome of 23 Mb, but nonetheless, approximately 14% of its total DNA derives from TEs, falling within 240 different families, several of which appear to have been introduced by horizontal transfer (123).

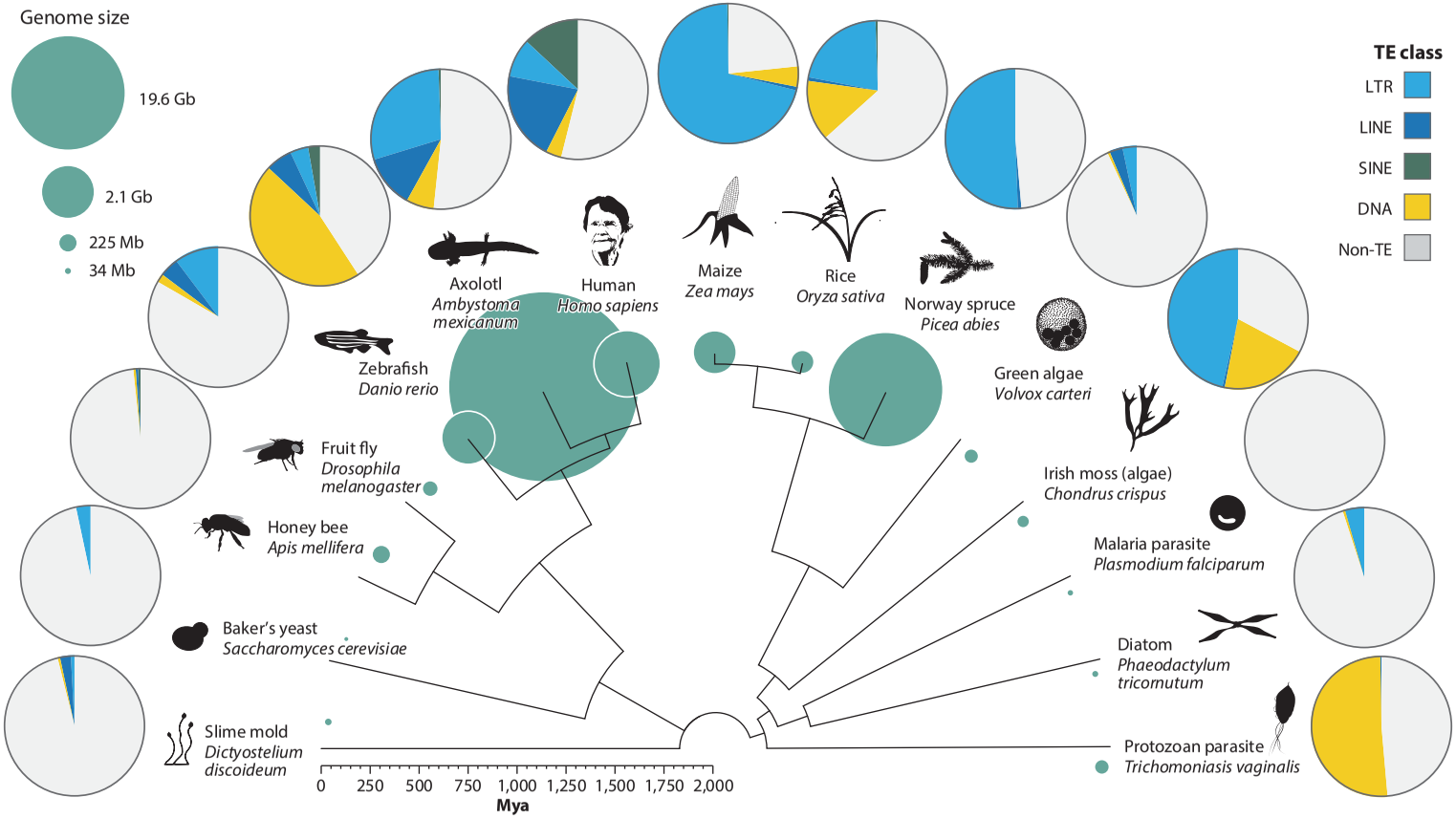


Figure 3

Distribution of TEs across the eukaryote phylogeny. Reference genome size (*sea green circles*) varies dramatically across eukaryotes and is loosely correlated with TE content. Here, the honey bee TE content is likely an underestimate, as approximately 3% of the genome derives from unusual large retrotransposon derivatives (39). For ease of visualization, YR retroelements have been included with LTRs and all class II elements are included under DNA. Data were acquired from genome RepeatMasker output files. Figure adapted with permission from Huang et al. (71); the *Volvox carteri* silhouette was provided by Matt Crook. Abbreviations: LINE, long interspersed nuclear element; LTR, long terminal repeat; SINE, short interspersed nuclear element; TE, transposable element; YR, tyrosine recombinase.

At the other end of the spectrum, many salamanders have undergone extreme genome expansions of as much as ∼120 Gb since diverging from other amphibians, predominantly through the accumulation of LTR retroelements (37, 118, 150). Plant genomes, too, often grow very large through the rapid accumulation of LTR elements (1, 36, 151). Although this expansion is usually due to the combined effect of numerous families, in the absence of repression, individual TEs can have drastic effects on genome size: Brown hydras diverged from the green hydra approximately 36 million years ago, but their genomes have roughly tripled in size in that time from ∼300 Mb to ∼1 Gb, largely due to the activity of a single family of *CR1* non-LTR elements (164).

The rate of nonessential DNA removal is also a critical factor shaping TE content and genome size. Genomic gigantism in salamanders is associated with low deletion rates, whereas in rice and *Arabidopsis*, transpositional gain of DNA appears to be buffered by high rates of deletion via ectopic recombination (30, 56, 107, 149, 150). This phenomenon is also apparent in birds and mammals and suggests an accordion model for genome size evolution, whereby bursts of TE activity promote the subsequent deletion of nonessential DNA via nonallelic recombination between recently duplicated TE copies (79, 124).

Transposable Element Diversity

In addition to varying abundance, there are also differences in TE diversity between species. This can be measured at different levels, from the number of classes or subclasses (class I/II, LTR/DDE-type, etc.) to the number of superfamilies, families, and subfamilies. Family substructure can occur when, as with *L1*, arms races develop between the TE and its host, driving the expansion of new subfamilies (46, 73). Other elements such as *Helitrons* produce subfamilies due to the acquisition of gene fragments and other host-derived DNA (153).

Regardless of how you measure it, many eukaryotes possess extraordinarily diverse TE repertoires. Zebrafish deserves a special mention here as both the most TE-abundant and -diverse vertebrate model organism currently in use, harboring nearly 2,000 distinct families with representatives from every subclass and almost every superfamily discussed in this review (**Figures 2** and **3**). Of these, DNA transposons are especially prevalent, with more than 1,000 families spanning a broad range of ages; this is unusual among fish and even closely related cyprinid species (59, 69, 140).

One might expect large genomes to be associated with wide TE diversity, but this is not always the case. Spruce pine, for example, is a gymnosperm conifer with a 20-Gb genome dominated by a relatively small number of very high copy number LTR elements. Remarkably, the vast majority of insertions are estimated to be between 5 and 60 million years old, which stands in contrast to rice and maize (**Figure 3**), where all insertions are less than 5 million years old (107, 119, 146). This indicates that while TE diversity is low in the spruce pine, as measured by the number of distinct families, elements that do establish themselves in the genome are removed slowly. The opposite is true of most flowering plants, which tend to have smaller genomes but more diverse TE landscapes than gymnosperms; for reasons that are unclear, across all land plants there is a negative correlation between genome size and TE diversity (38).

HOW THE BIOLOGY OF TRANSPOSABLE ELEMENTS AFFECTS THEIR SUCCESS

The fate of a TE family is dictated by three dynamic forces: (*a*) the rate of transposition, (*b*) the rate of fixation of new TE insertions, and (*c*) the rate at which TE sequences are deleted or eroded. Each of these processes is influenced by a multitude of factors that fall into two broad categories:

those intrinsic to the TE itself and those intrinsic to the host (genetics, development, physiology, etc.). Both TE and host factors are in turn shaped by the environment, and the resulting interplay between TE, host, and environmental factors results in the dazzling variety of TE landscapes in eukaryotic genomes. In the following section, we concentrate on the factors intrinsic to TEs that influence their survival and success within genomes.

Transposable Element Insertion Preference

A critical determinant of the fate of a TE is where it initially inserts in the genome. The most accurate way to study insertion preference is through the mapping of de novo insertions prior to the action of natural selection. Such studies have documented three general patterns: (*a*) TEs with apparently little insertional bias, (*b*) TEs favoring insertion in genomic regions that minimize their deleterious effects, and (*c*) TEs targeting sites that likely facilitate their subsequent propagation. We illustrate each with a few examples (but for an excellent recent review on TE targeting, readers are referred to 148).

Mechanistically, where a TE inserts is dictated by the nuclease that catalyzes its chromosomal integration. Because all TE-encoded nucleases (endonucleases, INs, transposases) have some degree of substrate specificity for particular DNA or chromatin attributes (e.g., sequence composition and nucleosome position), it follows that virtually all TEs show some level of insertion specificity. At the lowest level of specificity are TEs with nucleases that recognize highly degenerate or short sequence motifs, such as *L1* elements (45). Indeed, *L1* insertion profiles in human cells approach random distributions (54, 147).

Many TEs show much stronger insertion site biases, and a common theme involves targeting genomic sites where insertions are unlikely to disrupt cell function. A classic example involves several families of LINEs (e.g., R1, R2, etc.), which precisely target ribosomal RNA (rRNA) gene arrays (34). Such high copy number genes offer an excellent niche for TEs because insertion in one or a few of the genes is unlikely to have immediate deleterious consequences, and TEs can be progressively purged by recombination within the array. Precise targeting of these genes is achieved through the highly sequence-specific endonucleases encoded by these elements. Remarkably diverse R2-like families have evolved different site preferences within rRNA genes, which enables them to coexist within the same genome (90). The omnipresence of rRNA-targeting elements across metazoans attests to the evolutionary stability of this strategy.

Targeting safe havens enables TEs to colonize compact genomes with little intergenic space. For example, all TEs in the budding yeast *Saccharomyces cerevisiae* are LTR elements that have evolved integration strategies to avoid genes (148). *Ty1* and *Ty3* preferentially insert upstream of Pol III-transcribed genes, where they usually do not disrupt gene expression. This is an evolutionary convergence because *Ty1* and *Ty3* belong to two very different superfamilies (**Figure 2**) and achieve targeting via interaction of their IN with different Pol III subunits (14, 86). *Ty5*, which colonizes the genome of a closely related yeast, *Saccharomyces paradoxus*, favors integration within silent chromatin primarily at telomeric regions through yet another molecular interaction between its IN and, in this case, Sir4p chromatin factor (166).

A wide variety of TEs are known to target the 5′ upstream region of genes, which underscores the evolutionary benefit of this strategy for TEs (and potentially for the host). While insertion in this compartment may occasionally modulate the expression of adjacent genes, it reduces the probability of disrupting coding sequences and places the newly inserted TE in a chromatin environment that promotes its further expression, and thus transposition. Diverse DNA transposons have adopted this strategy, including the *P*-element in *D. melanogaster* (145), *MuDR* in maize (101), *mPing* in rice (116), and *VANDAL21* in *Arabidopsis* (131). The fission yeast retrotransposon *Tf1*

also targets promoter regions, but with a preference for a distinct subset of genes. Selectivity is achieved through *Tf1* IN interaction with specific host transcription factors (97). Remarkably, *Tf1* insertion around these genes can modulate their expression with adaptive effects in response to environmental stress (41).

Ty1/copia-like retrotransposons in *Arabidopsis* and possibly other plants have also evolved a mechanism to favor insertion into a subset of nonessential genes (131). This is achieved by targeting nucleosomes containing the histone variant H2A.Z, which are depleted within essential genes but enriched at a subset of environmentally responsive genes. As with *Tf1* in fission yeast, this observation suggests a nonrandom process of mutagenesis that could facilitate host adaptation in changing environmental conditions.

Another mitigating strategy is for TEs to target other TEs. Accordingly, several TE families have been found to be preferentially nested within other TE families (75, 99, 146). In most cases, it is difficult to distinguish between true targeting and the effects of differential retention of insertions due to selection. However, in the case of the non-LTR element *Tx1L* in *Xenopus laevis*, which is almost exclusively found within *Tx1D* DNA transposons, targeting is achieved through the sequence-specificity of the *Tx1L* endonuclease (24). Consequently, the fate of *Tx1L* is dependent on the success of another TE—a form of hyperparasitism.

Features Affecting the Long-Term Retention of Transposable Elements

All new TE insertions are subject to natural selection acting at the level of host fitness. The three main mechanisms underlying the deleterious effects of TE insertions are disruption of gene expression; toxic effects of TE products (nucleic acids or protein); and increased frequency of ectopic recombination between copies of the same TE family, which triggers gross chromosomal rearrangements (12).

While TE products can certainly be harmful—for example, accumulation of *L1* transposition intermediates has been implicated in Aicardi-Goutières syndrome (152)—toxicity does not appear to be a major driver of selection against TE accumulation. Instead, current data point to ectopic recombination as the predominant factor limiting TE accumulation in various species (12), albeit with some exceptions (141, 165). If this model is correct, then longer TEs should be strongly selected against due to their increased likelihood of initiating recombination. Indeed, LTR and LINE retroelements tend to fix and cluster in regions with low recombination rates (e.g., pericentromeric heterochromatin), while shorter elements such as SINEs and MITEs accumulate in gene-rich regions, which are generally characterized by higher recombination rates (22, 33, 165). The relationship between TEs and recombination is a complex one, however, and is discussed in more depth elsewhere (81).

A second important factor driving differential patterns of retention between TE types is their potential effect on gene expression. Since autonomous elements carry their own promoters and regulatory elements, they have a greater likelihood of disrupting the expression of nearby genes upon insertion. In the human genome, *L1* and many LTR elements are significantly depleted within genes and more severely so when considering insertions in the same orientation as the gene (112). Furthermore, older LTR insertions are also depleted in 5-kb windows surrounding genes—an observation that is consistent with strong selection acting against the effect of LTR promoters on host gene expression. For those TEs that fall within introns in mouse and human genomes, there is a significant depletion of insertions in hazardous zones near the intron/exon boundaries. In humans most, if not all, intronic TE insertions that cause disease are found within these exon-flanking regions (172).

Horizontal Transposon Transfer

Sex provides the primary mechanism for the spread of TEs within populations, but horizontal transfer of TEs (HTT) is another important factor in their long-term success, and one which occurs regularly on evolutionary timescales (60). All major groups of TEs undergo HTT, but it is particularly common for some families. Notably, many DDE-type DNA transposons appear to pass between species with relative ease, whereas HTT events involving non-LTR retroelements are rare in comparison (126, 134, 171).

One possible explanation for this is that some DNA transposons have evolved mechanisms that reduce their dependence on specific host factors. For example, they encode either weak or no promoters: this makes them dependent on insertion near host regulatory elements for expression but potentially reduces their dependence on specific transcription factors (60). This hypothesis has recently been tested using three elements from the Tc1/*mariner* superfamily, which share similar AT-rich, blurry promoters. These promoters drive reporter gene expression in cells derived from distantly related eukaryotes, in contrast to promoters isolated from an LTR retroelement and a *hAT* DNA transposon with more specific patterns of expression (122). Furthermore, the Tc1/*mariner* transposases are also known to be catalytically active in a wide range of organisms and even in cell-free assays. It is easy to envision how these properties could facilitate the spread of Tc1/*mariner* between widely diverged taxa (171).

The nature of transposition intermediates may also explain why some TEs can propagate horizontally more efficiently than others. DNA intermediates circularized and/or covalently bound by transposases or INs are likely to be more stable than the ribonucleoprotein complexes mediating TPRT of non-LTR retroelements. The formation of cytoplasmic capsid- and (sometimes) envelope-coated viral-like particles by LTR elements may also facilitate their propagation between and outside of cells (85, 125, 156). Likewise, where these intermediates occur and traffic within cells will also affect their propensity to access potential vectors for HTT, such as viruses (134, 156). Elements with intermediates targeted (non-LTR) or even confined (DNA transposons) to the nucleus will be less likely to insert within viruses that replicate exclusively in the cytoplasm (e.g., poxviruses) but more likely to jump into those that replicate in the nucleus (e.g., herpesviruses and baculoviruses). Thus, one can see how the intrinsic characteristics of TEs have a profound influence on their ability to propagate not just within but also between species.

Circumventing Host Defense Systems

Numerous host-encoded systems control TE activity, the existence of which often manifests in signatures of genomic conflict: for example, as mentioned previously, *L1* elements in placental mammals produce distinctive ladder-like phylogenetic trees (143, 144). These unusual trees are thought to arise from successive rounds of repression and mutational escape of elements from the defensive Krüppel-associated box (KRAB) zinc-finger protein family, such that only one or two *L1* subfamilies are active at any given time (46, 73).

This conflict is particularly intense in the germ cells, where dedicated silencing mechanisms such as the Piwi-interacting RNA (piRNA) system exist (3, 27), and has led to inventive strategies by TEs to escape repression. One spectacular example is that of *I*-elements in *D. melanogaster* oogenesis (159). *I*-elements preferentially retrotranspose in the oocyte, but their RNA intermediates are exclusively produced in the nurse cells that surround the developing oocyte before being trafficked into the mature oocyte via microtubule-mediated transport (155). Nurse cells are highly polyploid and outnumber the oocyte by fifteen to one, so this strategy allows *I*-element RNA to

reach much higher concentrations than would be possible through expression in the germ cells alone, whilst simultaneously limiting their exposure to piRNA silencing.

CONCLUSIONS

In the preceding pages, we have covered a minuscule fraction of the rich literature documenting the mechanisms by which TEs propagate, diversify, and interact within their hosts. TEs exist in all domains of life, but their abundance and omnipresence in eukaryotes attest to their profound influence on genome architecture and organismal evolution. We know, for example, that TEs account for the majority of *cis*-regulatory DNA in the human genome introduced during primate evolution (74, 154) and that TEs have given birth to numerous proteins co-opted for mammalian physiology and development (13, 49, 57). Their movement, regulatory activities, and effects on genome integrity also cause a plethora of diseases and exacerbate the effects of many more (13, 25, 66).

Despite their fundamental importance, however, the discovery of TEs did not immediately transform genome biology. The first six decades following McClintock's (111) initial breakthrough in maize were dominated by the genetic and molecular characterization of a relatively small subset of active TEs with phenotypic effects in agriculturally important species and a handful of model organisms. This changed with the revolutionary advances in DNA sequencing that began in the early 2000s. The ability to rapidly generate sequence data triggered a major shift in TE research to today's genome-wide studies in which virtually all TEs residing within a genome can be identified, compared, and interrogated for their regulatory and transcriptional activities. These studies have revealed that while most TEs in any given species are inactive relics of past invasions, this steady accretion of repetitive DNA has been a major fuel for the evolution of eukaryotic genomes.

TE research continues to be predominantly concerned with understanding their large-scale effects on genome architecture and function (13). But it is important not to lose sight of the fact that we can only interpret these effects when armed with an understanding of the mechanisms underlying the propagation of the elements themselves. Many of these insights have come from genetic, mechanistic, and evolutionary studies of individual TEs. However, it seems that in recent years this type of research has been in decline relative to genome-wide studies that attempt to discern broad patterns from an amalgam of diverse TEs lumped into a few groups.

Yet, as we have illustrated throughout this review, no two TE families look or behave identically. As a result, the effects of TEs on their host genomes are as varied as the TEs themselves. It is therefore of paramount importance to continue cataloging and organizing TE diversity in a wide range of species. Detailed studies of the molecular mechanisms and cellular activities of individual elements should also be encouraged, with priority given to TEs from widespread yet poorly characterized groups, such as *Helitrons*, *Mavericks/Polintons* or YR elements. Inroads through the less-traveled genomes are bound to uncover entirely new types of TEs and novel transposition strategies. While genomes are often dominated by defective and immobile elements, today's technology offers the ability to revive these elements and reveal the idiosyncratic features that make each TE uniquely fascinating.

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