

Transposable Elements, Epigenetics, and Genome Evolution

Nina V. Fedoroff

Transposable genetic elements (TEs) comprise a vast array of DNA sequences, all having the ability to move to new sites in genomes either directly by a cut-and-paste mechanism (transposons) or indirectly through an RNA intermediate (retrotransposons). First discovered in maize plants by the brilliant geneticist Barbara McClintock in the mid-1940s, they were initially considered something of a genetic oddity (1, 2). Several decades later, TEs acquired the anthropomorphic labels of “selfish” and “parasitic” because of their replicative autonomy and potential for genetic disruption (3, 4). However, TEs generally exist in eukaryotic genomes in a reversibly inactive, genetically undetectable form we now call “epigenetically silenced,” whose discovery can also be traced to McClintock’s elegant genetic studies (5, 6). As the underlying biochemical mechanisms emerged from obscurity and epigenetics became popular toward the end of the 20th century, it was proposed that epigenetic silencing evolved to control the proliferation of TEs and their perceived destructive potential (5, 6).

Today, we know that TEs constitute more than half of the DNA in many higher eukaryotes. We know, too, that the fingerprints of TEs and transposition are everywhere in their genomes, from the coarsest features of genomic landscapes and how they change through real and evolutionary time to the finest details of gene structure and regulation. My purpose here is to challenge the current, somewhat pejorative, view of TEs as genomic parasites with the mounting evidence that TEs and transposition play a profoundly generative role in genome

evolution. I contend that it is precisely the elaboration of epigenetic mechanisms from their prokaryotic origins as suppressors of genetic exchanges that underlies both the genome expansion and the proliferation of TEs characteristic of higher eukaryotes. This is the inverse of the prevailing view that epigenetic mechanisms evolved to control the disruptive potential of TEs. The evidence that TEs shape eukaryotic genomes is by now incontrovertible. My thesis, then, is that TEs and the transposases they encode underlie the evolvability of higher eukaryotes’ massive, messy genomes.

Although my examples in this essay are largely from plants, I believe that the inferences drawn apply to higher eukaryotes in general, among which plants tend toward exaggeration in genome size, TE abundance, and epigenetic complexity. Perhaps because they have no recourse to behavioral responses in coping with stressful environments, plants appear to have honed genetic and epigenetic strategies for adaptation to a much greater extent than animals.

How Transposons Came to Be Called “Selfish” DNA

The invention of DNA sequencing techniques in the late 1970s and their subsequent mechanization led to an explosion of knowledge about the structure, gene content, and organization of genomes. The 1960s had seen the development of nucleic acid reassociation techniques whose applica-

tion revealed the presence of much repetitive DNA in eukaryotic genomes (7, 8). As DNA sequencing became a reality, a good deal of

discussion arose over the value of sequencing entire genomes, particularly that of humans (9–12), in view of the calculation that only a tiny fraction of the genome consisted of genes in the then-conventional sense of protein- and structural RNA-coding sequences and their associated regulatory sequences (13).

A pair of papers published in *Nature* in 1980 solidified the idea that much of eukaryotic DNA, including transposons, was “junk”—a designation conferred a decade earlier by Ohno, who argued that our genomes were replete with nonfunctional DNA (3, 4, 14). The objective of the *Nature* papers was to get beyond the then

I contend that it was precisely the evolution of prokaryotic epigenetic mechanisms to regulate homologous recombination within the eukaryotic genome that made it possible for genomes to grow.

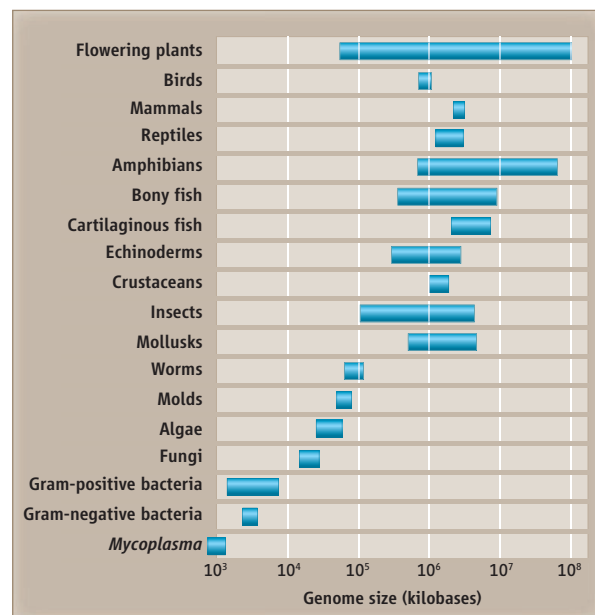


Fig. 1. The C-value paradox. The range of haploid genome sizes is shown in kilobases for the groups of organisms listed on the left. [Adapted from an image by Steven M. Carr, Memorial University of Newfoundland]

Nina V. Fedoroff is Distinguished Professor of Biosciences at the King Abdullah University of Science and Technology, Saudi Arabia, and Evan Pugh Professor in the Huck Institutes of the Life Sciences, Pennsylvania State University. She served as the Science and Technology Adviser to the Secretary of State and to the Administrator of the U.S. Agency for International Development (USAID) from 2007 to 2010. She was president of AAAS from February 2011 to February 2012. This article is based on the Presidential Address she delivered at the AAAS annual meeting in Vancouver, BC, on 16 February 2012. E-mail: nvf1@psu.edu

still-prevalent view that every bit of an organism's DNA has a specific function crafted by selection. Thus, both papers promoted Dawkins' concept of "selfish DNA"—the notion that DNA capable of proliferating within a genome, as TEs do, may need no other explanation for its survival (15). Orgel and Crick asserted, "The spread of selfish DNA sequences within the genome can be compared to the spread of a not-too-harmful parasite within its host" (3).

The selfish DNA concept was initially offered to explain the long-standing C-value paradox that organisms of similar evolutionary complexity differ vastly in their DNA content (16), and this it did. The C value, which

is the DNA content per haploid genome, varies widely among closely related organisms of apparently comparable complexity (Fig. 1); this has for some time been attributed to the repetitive portion of the genome (17). Such variation is especially striking in angiosperms, whose highest and lowest C values differ by a factor of 2000 (18, 19). The explanation of the C-value paradox does indeed reside largely in the profound differences among genomes in the abundance of TEs, primarily retrotransposons, even as gene numbers remain relatively constant. The *Arabidopsis* genome, for example, contains about 27,000 genes and 20 to 25 Mb of retrotransposons, whereas the maize genome contains about 40,000 genes and more than 1800 Mb of retrotransposon sequences (20–22). What the selfish DNA hypothesis does not attempt to explain, however, is how genomes can accumulate such vast amounts of repetitive sequences, given the ease of eliminating them by homologous recombination.

The Selfish DNA Label Stuck

Fortunately, genome sequencing raced forward, and today we have a vastly more complex understanding of genome structure and organization than we might have had if sequencing had been restricted to protein- and RNA-coding sequences. But we find ourselves neck deep in TEs: Transposon and retrotransposon sequences constitute two-thirds of our own genome and 85% of

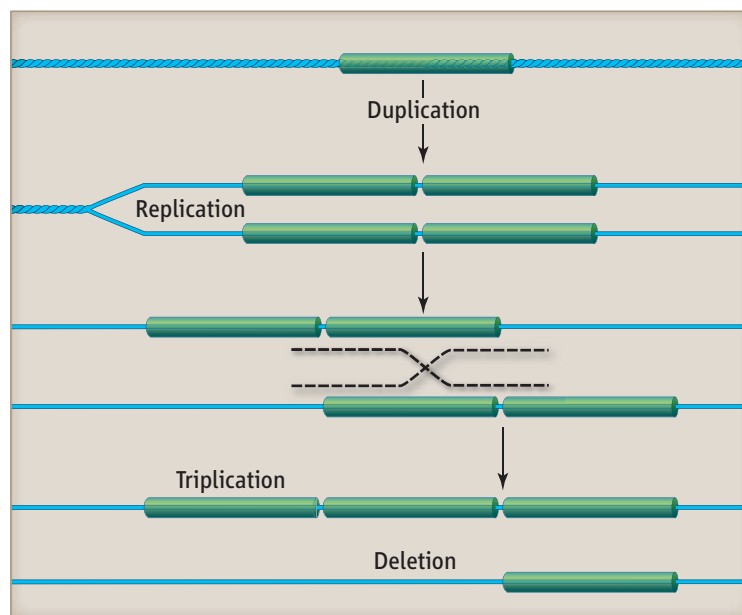


Fig. 2. Generation and elimination of duplications by unequal crossing over. Broken lines trace the recombination event.

the corn genome (21, 23). Ideas about junk DNA have evolved substantially over the past two decades, with growing knowledge of the regulatory roles fulfilled by noncoding sequences and their transcripts (24, 25). However, the transposon monikers from the selfish DNA papers have persisted. Having cloned the first mammalian DNA methyltransferase gene and realizing that its methyltransferase domain resembles those of prokaryotic restriction methyltransferases, Bestor proposed in 1990 that eukaryotic DNA methylation had evolved to regulate gene expression in development and chromosome structure, much along the lines of earlier proposals (26–28). But by the end of the decade, he and his colleagues had concluded that because cytosine methylation is predominantly found in TEs, methylation was more likely to represent a nuclear defense system that had evolved precisely to “control” the destructive potential of “parasitic sequences,” mostly transposons and retrotransposons (5, 29). This view was widely accepted, and transposons are today almost universally referred to as “invaders,” “parasites,” or “parasitic sequences” (30–33).

Does the notion that epigenetic mechanisms evolved to control invading “parasitic” transposons still fit the facts in

the light of the many that have accumulated since this hypothesis was first advanced? Perhaps not. The difficulty starts with the question of where such parasites might have come from. It turns out that genes encoding transposases, which all have certain common structural motifs in their catalytic cores, are present throughout eukaryotes (34) and can be traced back into prokaryotic organisms that do not have the elaborate epigenetic regulatory superstructure of eukaryotes (35). That is, transposons were around long before the eukaryotic lifestyle, with its bloated genomes, appeared on the evolutionary scene. This implies that transposons

coevolved with all the rest of the eukaryotic genome's inhabitants. Moreover, prokaryotic transposition is minimized and regulated by mechanisms that are similar to those in eukaryotes, including weak, enhancer-insensitive promoters, transposon-encoded regulatory proteins and regulatory RNAs, and DNA methylation (36–39). Yet prokaryotic genomes carry only modest numbers of transposons.

I argue that transposable elements accumulate in eukaryotic genomes because of, not despite, epigenetic silencing mechanisms.

It is true that the ability of eukaryotic transposons and retrotransposons to accumulate in large numbers, together with their highly generic transposition mechanisms, means that the proliferation of a transposon introduced into a genome lacking it—whether by a genetic cross or a virus—makes it resemble an “invader” (40, 41). And indeed, there is growing appreciation that transposons are subject to horizontal transfer in eukaryotes, in some cases through host-parasite interactions (42–46). But the same is true of prokaryotic transposons (37). As well, new transposons can arise within a genome and silent transposons can be mobilized anew by a variety of physiological and genetic stresses, undergoing “bursts” of transposition to expand genomes over millennia before being silenced and decaying (47) or being silenced quickly within a generation (48).

to cause major, even catastrophic, chromosomal rearrangements?

What Epigenetic Mechanisms Do and How They Came to Be

I believe that the answer to these questions lies precisely in the epigenetic mechanisms that eukaryotes have elaborated to a much greater extent than prokaryotes. Repressive protein complexes, histone methylation, RNA interference (RNAi), and RNA-directed DNA methylation, as well as recombinational regulatory complexes, are among the epigenetic mechanisms that have so far surfaced (55–59). These serve a variety of structural and regulatory functions, but perhaps the essential one for understanding the evolution of eukaryotic genomes is the minimization of illegitimate and ectopic recombination among homologous sequences during DNA replication and the DNA break-repair processes that maintain genome and chromosome stability.

Heterochromatin, the highly compacted chromosome regions rich in repetitive DNA, is recombinationally inert (60, 61). Although not all eukaryotes use all of the known epigenetic mechanisms, even lower eukaryotes with relatively small genomes use RNAi to stabilize repetitive DNAs, such as ribosomal RNA genes and centromeric repeats (61–63). In fission yeast, noncoding transcripts of repetitive sequences initiate a process that generates small RNAs, which in turn target further transcripts for degradation and attract protein complexes that induce heterochromatinization through histone modification (64, 65). Disruption of the RNAi machinery disturbs the repair of double-strand breaks, stimulating repair by homologous recombination (66).

The evolutionary origins of the eukaryotic epigenetic regulatory machinery lie in bacterial systems that discriminate endogenous DNA from that acquired through horizontal gene transfer and bacteriophage infection (67–69). Although prokaryotic transposons can move both by conjugation (commonly on plasmids) and on bacteriophage, they do not appear to have been independently targeted for inactivation by either the restriction-modification system or the CRISPR (clustered regularly interspaced short palindromic repeat)–*cas* (CRISPR-associated) interference pathway (70). This recently discovered bacterial pathway confers sequence-specific immunity to phage and plasmids and exhibits parallels with eukaryotic RNAi systems, particularly the Piwi-interacting RNA

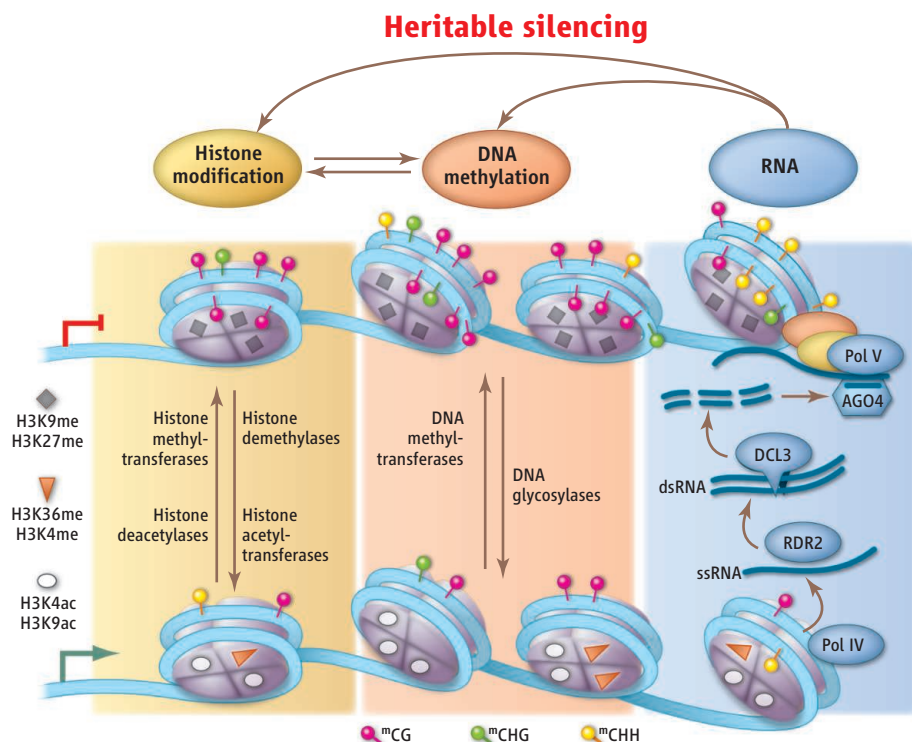


Fig. 3. Plant epigenetic mechanisms include DNA methylation, histone modification, and RNA-directed DNA methylation (RdDM). RdDM involves two plant-specific RNA polymerases (Pol IV and Pol V), an RNA-dependent RNA polymerase (RDR2), an enzyme that cleaves double-stranded RNA (DCL3), and an Argonaute-family RNA-binding protein (AGO4). [Adapted with permission from (199)]

How Do Genomes Get So Fat?

There's perhaps a deeper problem than the ancient origin of transposons. What distinguishes the organization of higher eukaryotic genomes from that of prokaryotes is the presence of vast amounts of duplicated DNA. It has long puzzled me that we almost universally take this for granted. But then, eukaryotes also have a markedly more complex, largely epigenetic system than do prokaryotes for managing the transcription, reproduction, and recombination of genetic material, as well as its distribution to daughter cells during mitotic and meiotic divisions. Which is cause and which is effect?

Prokaryotes can readily duplicate genome segments by virtue of small stretches of homology, but tandem duplications are rapidly lost unless retained by selection, and even then, they are generally interspersed with nonhomologous sequences (49–51). This is illustrated diagrammatically in Fig. 2. Absent either selection or a reduction in homology, tandem duplications are inevitably eliminated by homologous unequal intra- or interchromosomal crossing over between duplicated sequences, generating one-copy organisms (an absorbing state) and organ-

isms with increasing numbers of copies that in turn throw off singletons (50, 52). Organisms with many copies are quite unstable and are likely to be eliminated, either by virtue of the energetic drag of the extra DNA or by a population bottleneck. This is borne out by the observation that duplicate genes in prokaryotes are generally acquired by horizontal gene transfer rather than by duplication (53, 54).

The "selfish DNA" argument rests on the assumption that there exists a category of DNA that has little or no phenotypic effect, and hence is not subject to selective pressure, but can nonetheless multiply within the genome. This is not an unreasonable inference, because we know that eukaryotic genomes are packed with repetitive DNA of all kinds. But I find it quite remarkable that it passes unremarked. How did eukaryotes tip the balance between duplication and deletion that keeps genome size small in organisms in which homology-dependent recombination mechanisms predominate? And how can transposons, whose duplicative mechanisms create dispersed repetitive sequences, build up in large numbers, given the ability of homologous recombination among them

system of *Drosophila* (71, 72). Cytosine methylation is widespread in both prokaryotes and eukaryotes, and eukaryotic DNA methylases evolved from bacterial restriction-modification methylases by acquiring new recognition and binding modules (69). The evolution of DNA methylases appears to have proceeded in parallel with that of histone-modifying enzymes and RNA-based silencing mechanisms, so that today they comprise intimately interconnected systems (68, 69). Some eukaryotes lack either DNA methylation or the RNAi machinery (or both), but nonetheless exhibit epigenetic silencing; hence, there is some redundancy among silencing mechanisms (73, 74). Precisely how these disparate systems came together is not yet known, but the evolutionary genius of linking RNAi feedback mechanisms to the heritability of the DNA methylation mechanism means, of course, that silencing can be inducible, sequence-specific, and heritable.

My contention is that it was precisely the evolution of prokaryotic epigenetic mechanisms, originally limiting recombination among horizontally exchanged sequences, to regulate homologous recombination within the eukaryotic genome that made it possi-

ble for genomes to grow. Interference with DNA methylation, histone modification, and the small RNA pathways of contemporary genomes generally destabilizes repetitive regions, both tandem and dispersed (48, 61, 62). The ability to suppress homologous recombination might well be what tipped the balance between duplication and deletion in favor of sequence endo-reduplication in general and transposon proliferation in particular. The fact that small diffusible RNA molecules are at the heart of the silencing machinery also means that new copies of transposons cannot evade regulation by moving to new locations where the ability to cause severe chromosomal disruptions through ectopic homologous recombination might consign them to the scrap heap of evolution. What I am suggesting, then, is that TEs accumulate in eukaryotic genomes because of, not despite, epigenetic silencing mechanisms. This is exactly the inverse of the “parasite control” hypothesis, which posits that epigenetic mechanisms arose to control invading, parasitic transposons (5).

The ability to retain duplicated sequences is also arguably a critical step in the evolution of multicellular organisms, underpinning

the ability to diversify duplicates for expression in specific cells and tissues, at different developmental moments, and in response to different environmental stimuli (75). Equally key is the ability to program genes for differential expression by a variety of mechanisms, among which are the relatively stable ones involving DNA and histone modification, as well as the more labile small RNA-mediated and transcriptional mechanisms. On balance, then, the likelihood that contemporary eukaryotic genomes evolved in the context of epigenetic mechanisms seems vastly greater than the likelihood that they were invented as an afterthought to combat a plague of parasitic transposons.

Plant Genomes Do It More

Plants have a more complex and redundant array of epigenetic silencing mechanisms than animals, making use of multiple DNA methylation mechanisms, chromatin protein modification, and feedback mechanisms involving small noncoding RNAs (55, 58, 76). Mammals primarily methylate the C residues in the CG dinucleotide context, whereas plants methylate C residues in nucleotides within all sequence contexts (55,

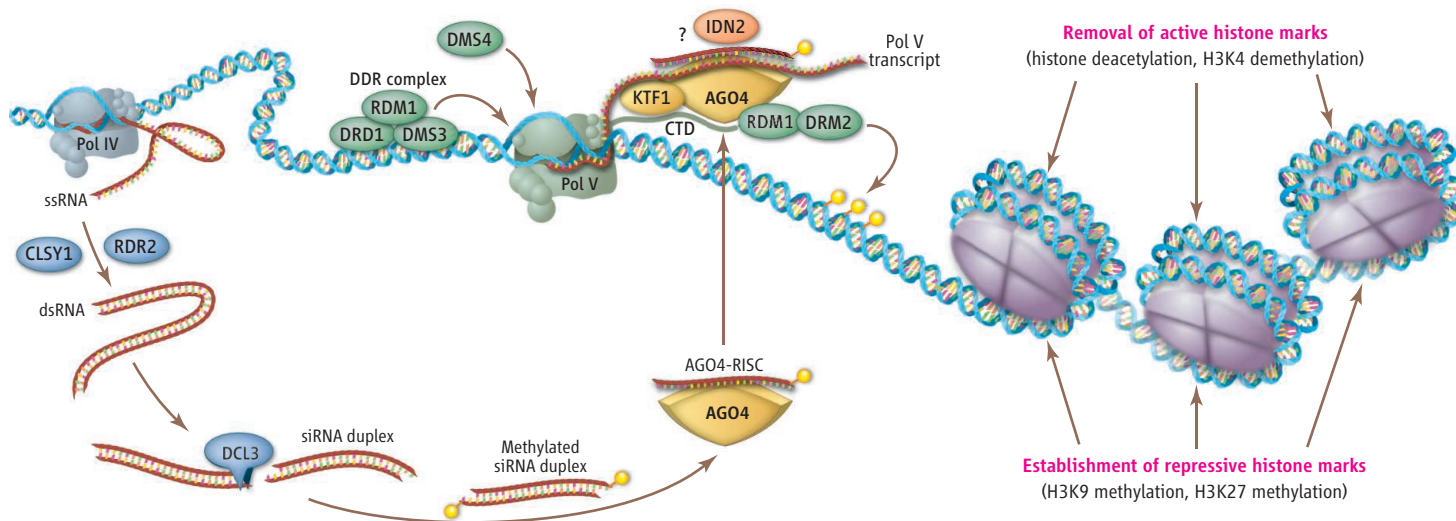


Fig. 4. The RNA-directed DNA methylation pathway. RNA polymerase IV (Pol IV) initiates RdDM, generating single-stranded RNA (ssRNA) that is then copied into double-stranded RNA (dsRNA) by RNA-DEPENDENT RNA POLYMERASE 2 (RDR2). The putative chromatin remodeler and/or helicase CLASSY 1 (CLSY1) assists in one or more of these steps. DICER-LIKE 3 (DCL3) cleaves the dsRNA into 24-nucleotide small interfering RNA (siRNA) duplexes that are then methylated at their 3' ends by HUA-ENHANCER 1 (HEN1). A single strand of the siRNA duplex associates with ARGONAUTE 4 (AGO4) to form an RNA-induced silencing complex (RISC)-AGO4 complex. Independently of siRNA biogenesis, Pol V transcription is assisted by the DDR complex [DRD1 (DEFECTIVE IN RNA-DIRECTED DNA METHYLATION 1), DMS3 (DEFECTIVE IN MERISTEM SILENCING 3), and RDM1 (REQUIRED FOR DNA METHYLATION 1)] and DMS4. AGO4 binds Pol V transcripts through base-pairing with the

siRNA and is stabilized by AGO4 interaction with the NRPE1 (the largest subunit of Pol V) C-terminal domain (CTD) and KTF1 (KOW DOMAIN-CONTAINING TRANSCRIPTION FACTOR 1), which also binds RNA. IDN2 may stabilize Pol V transcript-siRNA pairing. The RDM1 protein of the DDR complex binds AGO4 and the de novo cytosine methyltransferase DOMAINS REARRANGED METHYLTRANSFERASE 2 (DRM2), bringing them to Pol V-transcribed regions, resulting in DNA methylation. Histone modifications resulting from the RdDM pathway include the removal of activating acetylation and methylation marks [deacetylation of multiple Lys of several core histone proteins and demethylation of histone H3 Lys⁴ (H3K4)] and the establishment of alternative, repressive histone methylation marks (such as the methylation of H3K9 and H3K27), thereby facilitating transcriptional silencing. [Adapted with permission from (80)]

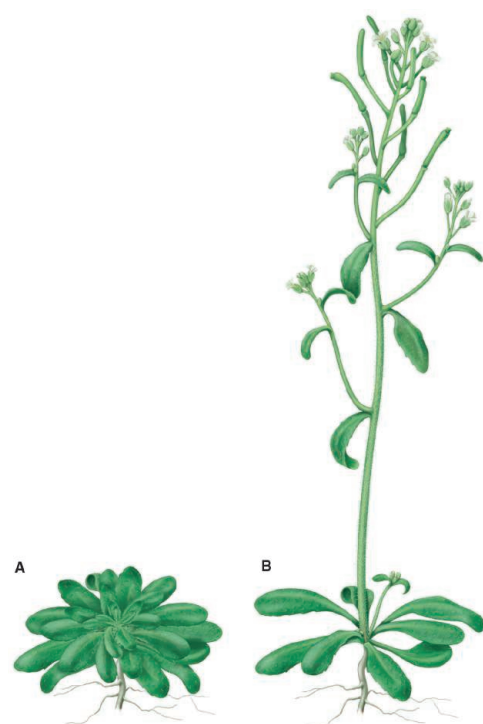


Fig. 5. Vernalization. *Arabidopsis* plants requiring vernalization grow vegetatively (A) unless exposed to a period of cold to induce flowering (B). Vernalization involves cold-induced epigenetic silencing of the *FLC* gene, a repressor of flowering.

77). DNA methylation stabilizes the silencing and inactivation of genes and other genetic elements in many eukaryotes, but is not universal; *Drosophila* and budding yeast represent well-investigated exceptions (55, 78). Chromosomal protein modification, particularly histone 3 methylation, is involved in guiding DNA methylases to their correct targets in both plants and animals (55, 79). In plants, unmethylated DNA is methylated by one DNA methyltransferase, whereas main-

tenance methylation involves two additional DNA methyltransferases (55). Figure 3 shows an overview of the several epigenetic mechanisms currently known to exist in plants.

Sequence specificity is imparted to DNA methylation through a mechanism called RNA-directed DNA methylation (RdDM) (57, 58). RdDM involves two unique plant RNA polymerases, Pol IV and Pol V, and is mediated by 24-nucleotide small interfering RNAs (siRNAs) (55, 57, 80). As illustrated in Fig. 4, RdDM is initiated by conversion of Pol IV-generated transcripts to RNA duplexes by an RNA-dependent RNA polymerase (RDR2). The duplexes are then cleaved into 24-nucleotide siRNAs by an RNase III-family enzyme (DCL3) and the appropriate strand associates with the Argonaute family protein AGO4 (55, 80, 81). This leads to the formation of a complex comprising the AGO4-siRNA and a number of other proteins (including a DNA methylase, DRM2), which then triggers local DNA methylation (57, 80, 82). As well, activation of RdDM promotes histone deacetylation and methylation changes that lead to the establishment of chromatin structures that repress transcription (57, 80). Plant DNA demethylation is mediated by one of several DNA glycosylase activities that removes the 5-methylcytosine, after which the DNA backbone is cleaved at the abasic site and repaired (83).

Why and exactly how the different epigenetic systems evolved remains to be understood. But plants use epigenetic systems today in a variety of developmental contexts. Unlike higher animals, plants do not set aside a germ line early in development;

this imposes more stringent requirements for maintaining genetic integrity, because differentiated genomes must eventually be reprogrammed for reproduction. So the elaboration of epigenetic mechanisms may have made possible the indeterminate lifestyle of many higher plants and their ability to reproduce in response to environmental signals. Epigenetic mechanisms, for example, regulate such environmentally responsive developmental transitions as vernalization, a cold-temperature requirement for germination or the transition to flowering, the reproductive phase. For example, *Arabidopsis* plants requiring vernalization grow vegetatively unless exposed to a period of cold to induce flowering, as illustrated in Fig. 5 (84, 85). Vernalization is mediated by cold-induced epigenetic silencing of the *FLOWERING LOCUS C (FLC)* gene that encodes a repressor of flowering. The silencing increases with the duration of the cold period, involves production of noncoding *FLC* transcripts, and results in histone modifications that inactivate transcription of the gene (86).

Although transposons are primary targets for epigenetic silencing, they are far from the only targets in plants. The first plant gene silencing mechanism understood at the molecular level was that underlying the long-known ability of a viral infection to cross-protect a plant against infection by a closely related virus (87–90). Then, in 1994, it was reported that a wholly artificial gene comprising a viroid cDNA became methylated and transcriptionally inactive in the tobacco genome, but only if viroid RNA replication had occurred, suggesting a feedback mechanism initiated by transcript overabundance (91). It was subsequently discovered in the early days of plant molecular modification that an introduced transgene encoding an

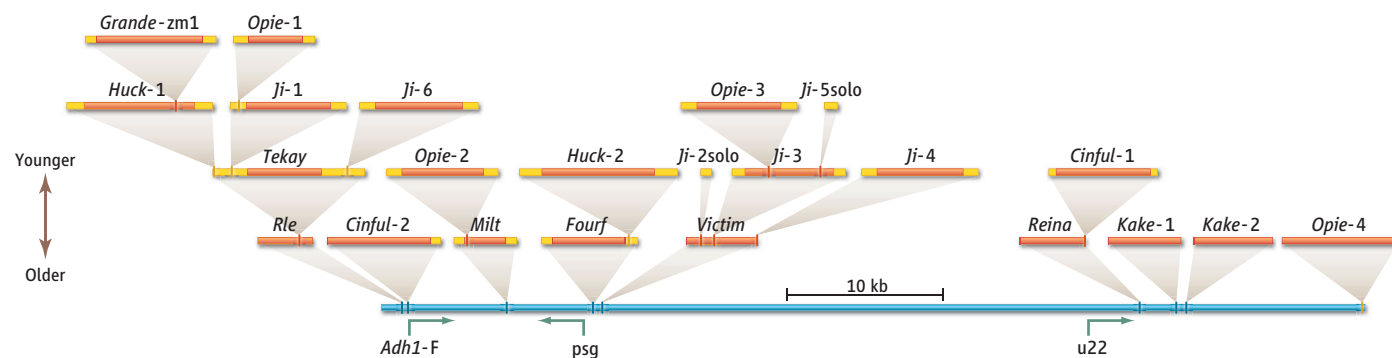


Fig. 6. The arrangement of retrotransposons in the maize *adh1-F* region. The short lines represent retrotransposons, with the internal domains represented in orange and the LTRs in yellow. Younger insertions within older insertions are represented by the successive rows from the bottom to the top of the

diagram. Small arrows show the direction of transcription of the genes shown under the long blue line that represents the sequence in the vicinity of the *adh1* gene. [Adapted with permission from (102)]

enzyme in the pigment biosynthetic pathway was subject to silencing (92–94). Later studies found that silencing entails both transcriptional and posttranscriptional mechanisms, and that these mechanisms share characteristics with those used by plants to control viral pathogens and are mediated by the production of siRNAs (95, 96). Sequence duplication also underlies a reversible silencing phenomenon, termed “paramutation,” in which an allele termed “paramutagenic” can heritably silence a susceptible allele termed “paramutable” of the same locus residing on the homolog (97). Paramutation involves a small RNA feedback mechanism and DNA methylation triggered by duplication of either coding or regulatory sequences (98, 99). Thus, the repetitive character of the sequence is also a common trigger for siRNA-mediated gene silencing and methylation (100).

The Contemporary Plant Genome Landscape

Despite the multiplicity of plant epigenetic silencing mechanisms, the fingerprints of transposition and recombination are evident at every level of plant genome structure, organization, and evolution. Maize genes are clustered in small groups separated by long, uninterrupted stretches of DNA consisting of retrotransposons (101, 102). Almost 85% of the contemporary 2.3-Gb maize (*Zea mays* or corn) genome comprises transposons, more than 75% of which are long terminal repeat (LTR) retrotransposons (21). Its roughly 40,000 genes, averaging about 3.3 kb in length, form small islands in a sea of more than a million transposons and retrotransposons belonging to almost 1300 different gene families.

In addition to forming very large blocks, retrotransposons exhibit a tendency to home to different neighborhoods. In maize, for example, *gypsy* and *copia* elements are over- and underrepresented in pericentromeric regions, respectively (21, 103). Within a retrotransposon block, younger elements are progressively nested within older elements, as illustrated in Fig. 6 for a short region near the maize *adh1* gene (21, 102, 103). Such targeting can occur through the interaction of retrotransposon-specific proteins and chromatin proteins, which are themselves preferentially associated with certain types of sequences. An example is provided by the interactions of yeast Sir4p, a structural protein of heterochromatin, with a 6-amino acid motif of the Ty5 integrase protein that targets insertion into telomeric heterochromatin (104, 105). An *Arabidopsis lyrata*

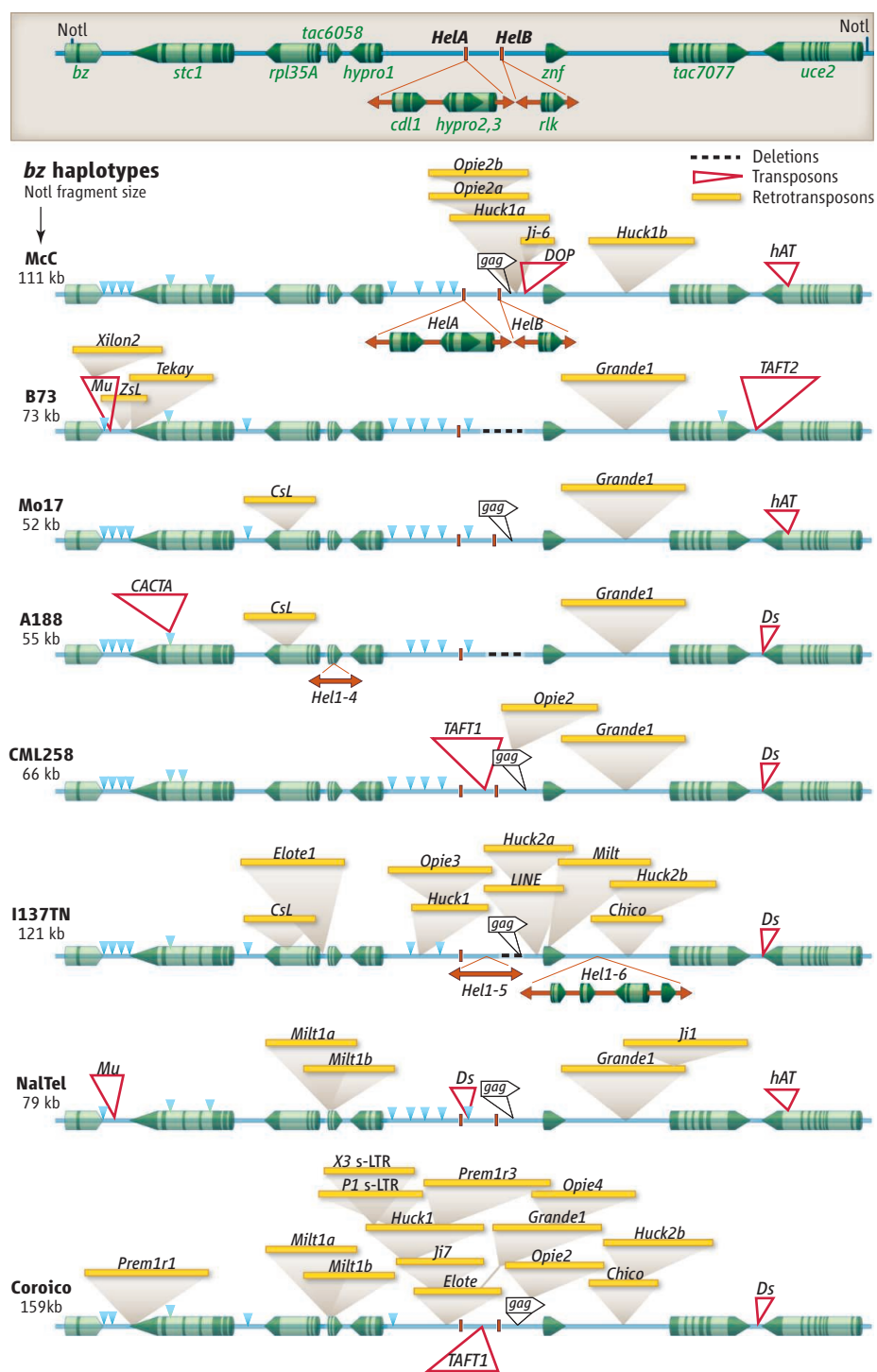


Fig. 7. The organization of the sequence adjacent to the *bronze* (*bz*) gene in eight different lines (haplotypes) of maize. The genes in this region are shown in the top diagram: *bz*, *stc1*, *rpl35A*, *tac6058*, *hypro1*, *znf*, *tac7077*, and *uce2*. The orientation of the gene is indicated by the direction of the green pentagon, pointing in the direction of transcription; exons are represented in dark green and introns in light green. Each haplotype is identified by its name and the size of the cloned *NotI* fragment. The same symbols are used for gene fragments carried by Helitrons (Hels), which are represented as bidirectional arrows below the line for each haplotype. Vacant sites for *HelA* and *HelB* are provided as reference points and marked by short vertical red bars. Dashed lines represent deletions. Retrotransposons are represented by yellow bars. DNA transposons and TAFTs (TA-flanked transposons), which are probably also DNA transposons, are represented by red triangles; small insertions are represented by light blue triangles. [Redrawn with permission from (113)]

centromeric retrotransposon was reported to insert preferentially into centromeres in *A. thaliana* (106). Because the centromeric sequences are quite different in the two species, targeting is likely to involve an interaction with the highly conserved centromere-specific structural proteins.

Unlike retrotransposons, which replicate through an RNA intermediate and reinsert DNA copies, DNA transposons move by a cut-and-paste mechanism, generally excising from just one newly replicated sister chromatid and reinserting into a site either nearby on the same chromosome or elsewhere in the genome (107). Because a copy of the transposon is retained at the donor site, such transposition events commonly give rise to additional transposon copies. DNA transposons account for a much smaller fraction of the plant genome than retrotransposons, are generally present in fewer copies, and tend to be associated with genic regions, some even inserting preferentially into genes (108). Mu transposons in maize favor recombinationally active regions of the genome (109), whereas Helitrons accumulate near but not inside each other (110). Such clustering may reflect the propensity of some TEs to move to nearby sites, long documented for the *Ac/Ds* (*Activator/Dissociation*) transposon family of maize (111).

The Rapid Pace of Plant Genome Change

Genome divergence through TE activity and recombination are ongoing processes that occur within species at surprisingly high rates. For example, a comparison among maize inbred lines revealed major differences within a region of just 150 kb surrounding the *bronze* gene in both TE abundance and composition (Fig. 7) (112, 113). Speciation—the process by which subgroups of a reproductively compatible population become reproductively isolated—occurs by a variety of mechanisms, some of which involve both transposon mobilization and active genome restructuring. The genomes of newly formed plant species are necessarily similar, and the gene order is largely colinear. As the evolutionary distance increases, the colinearity declines rapidly, although the number and nature of the genes remain more or less constant

(114, 115). Such evolutionary scrambling of genomes is illustrated in Fig. 8, which traces orthologous sequence blocks among familiar grass genomes (116).

It has long been known that genes change their chromosome locations, and it has been speculated that transposons mobilize large DNA segments because they are often found at the ends of inverted or transposed sequence (117–120). McClintock's initial studies on the *Ac/Ds* transposon family showed that chromosome breaks at the site of insertion of a nonautonomous *Ds* element could be resolved with attendant duplications, deletions, inversions, and translocations of large chromosomal segments (121, 122). More recent studies on *Ac/Ds*-associated rearrangements at the P locus identified transposition events that initiate at the 5' end of one transposon and terminate at the 3' end of a nearby transposon (123). Such "alternative transposition" events can generate a variety of rearrangements (depending on the relative orienta-

template slippage, and unequal crossing over (114, 124). Such duplications can arise during mitotic chromosome replication, when transposition is known to occur, by the alternative transposition mechanism. The well-known tendency of transposons of the *Ac/Ds* family to undergo short-range transpositions from only one sister chromatid to an unreplicated site nearby gives rise to genic regions flanked by copies of the same transposon, facilitating subsequent mobilization of the intervening chromosome segment (111, 123).

Genome Contraction and Divergence of Intergenic Sequences

Genomes expand by sequence duplication, transposition, and retrotransposition, and they contract by deletion mediated by a variety of homologous and illegitimate recombination events (125–129). Solo LTR generation by unequal homologous recombination between the LTRs at the ends of a single retroelement is frequent in some plant species, particularly near genes and at the kinetochore (126). Such unequal events can also occur between adjacent elements, leading to the deletion of the DNA between two TE copies (125, 126). Not surprisingly, retrotransposon elimination by unequal and illegitimate recombination is most frequent in recombinationally active genome regions (130). In parts of the genome where TEs are abundant, homologous recombination is markedly suppressed; this is likely a causal factor in TE accumulation, as noted earlier (131, 132).

Autonomous DNA transposons commonly decay by internal deletions that reveal the operation of double-strand break

repair mechanism that duplicates genetic information, now called "filler DNA," by the invasion of a single strand into a duplex nearby and copying of a short sequence that is then inserted at the deletion breakpoint (124). McClintock identified and investigated a series of *Spm* derivatives that originated from an internally deleted, nonautonomous *Spm*, all of which were the result of further deletions within the same element at the same location (133, 134). These arose at a high frequency, but only in the presence of an autonomous element; this finding suggests that they were initiated either directly

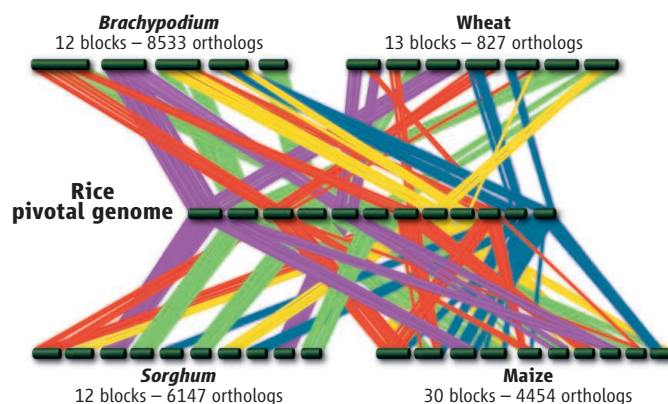


Fig. 8. Identification of orthologous sequence blocks in grass genomes. A schematic representation shows the 20,270 orthologs identified between the rice chromosomes used as a reference and the *Brachypodium*, wheat, sorghum, and maize chromosomes. Each line represents an orthologous gene. The blocks reflect the origin from ancestral protochromosomes. [Redrawn with permission from (116)]

tion of the transposon ends) and can translocate large segments of intervening DNA.

The movement of genes is often mediated by a process that duplicates the gene and flanking sequences, leaving a copy at the original insertion site (115). Because translocated genome segments are commonly flanked by transposons, the movement of a chromosome segment is likely to be initiated by a double-strand break at the new insertion site of a transposon and may be repaired through one of several known processes that repair double-strand breaks in plants, including synthesis-dependent strand annealing,

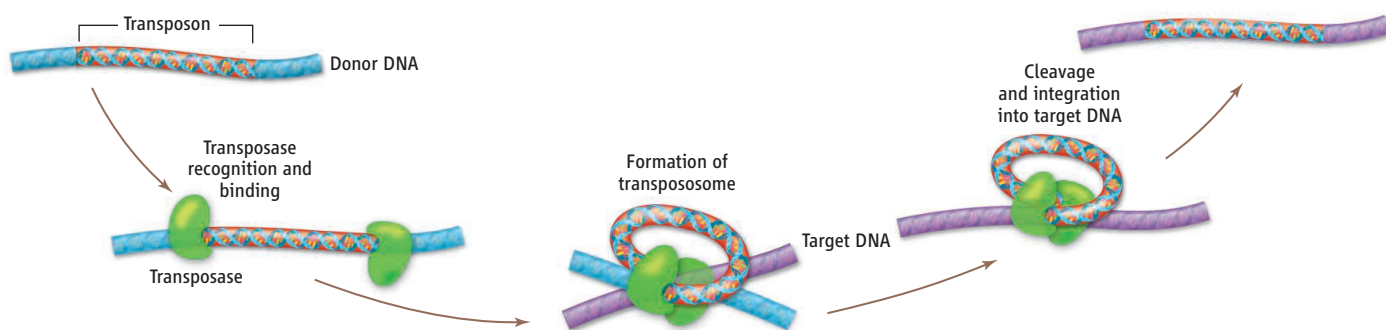


Fig. 9. DNA "cut-and-paste" transposition mechanism. Transposition is initiated by the site-specific recognition and binding of transposase to the transposon DNA ends. Dimerization of the transposase leads to formation of the transpososome,

which brings together the transposon termini and a target site. Concerted cleavage at the donor and target sites is followed by integration of the excised transposon into the target site and resection of the empty donor site (200).

by the double-strand cleavage activity of the transposase encoded by the autonomous element or indirectly by secondary double-strand breaks incurred during the transposition reaction (135).

Analyses of intergenic regions in related species have revealed that they turn over very rapidly on an evolutionary time scale. Fine-grained analysis of the sequence dynamics shows that the intergenic volatility is indeed mediated by transposons, which both delete adjacent DNA sequences and insert filler DNA from elsewhere in the process of repairing the double-strand breaks in the DNA introduced by transposases (128). Although deletions commonly occur adjacent to a transposon end, they can remove entire transposons. Statistically significant clustering of such deletions in the vicinity of transposons suggests that they arise as a result of the double-strand breaks that initiate transposition.

Traffic in Genes and Regulatory Sequences

At a much finer level of resolution, transposons contribute to creating genes, modifying them, and programming and reprogramming them. Many transposons and retroelements contain captured gene fragments and can be part of gene regulatory regions (136–142). A classic example is provided by the maize *R* locus that encodes a transcription factor necessary for synthesis of anthocyanin pigments. The *R-r* allele comprises four tandem duplications, including a complete coding sequence and several truncated ones in direct and inverted order separated by a *Doppia* transposon. The complete coding sequence is responsible for pigment expression in the plant, whereas the several truncated copies support pigment expression in the seed (143).

The traffic in genes and regulatory sequences is bidirectional: Transposons pick

up bits and pieces of genes that code for proteins other than transposases, and transposase genes are pressed into services other than transposition (144, 145). For example, the proteins encoded by the *FAR1* and *FHY3* genes of *Arabidopsis* are both related to the MuDR family of transposases (146). *FHY3* and *FAR3* are transcription factors that regulate light-dependent chlorophyll biosynthesis in development, the former also gating phytochrome signaling to the circadian clock (147, 148). A familiar example is provided by the human immune system, which uses recombinase proteins that evolved from transposases to generate sequence diversity through V(D)J recombination (149, 150). Transposons provide the telomeres of some organisms and jump in to replace them in others (151, 152). Centromeres contain and are often surrounded by transposons (22, 153–155). As well, transposons are central to the epigenetic phenomenon of "imprinting" that imbues genes with different expression patterns depending on whether they were transmitted through male or female gametes; such differences arise during the major epigenetic reprogramming events of gametogenesis (156–158).

Driving Evolution

Thus, transposases hold a special place in the pantheon of genome sculptors. Arguably the products of the most abundant genes on Earth (159), transposases are transposon-encoded enzymes that cleave transposon ends and attach them to new sequences. The essential elements are (i) very strict sequence recognition and precise cleavage at the donor site and (ii) either a relaxed sequence specificity or no sequence specificity at the target site (160). The prokaryotic Mu element's transposition mechanism appears to be paradigmatic and common to many members of the

transposase superfamily (161–165). Multimers of the transposase form a transpososome complex that recognizes the transposon's terminal inverted repeats and brings them together with the target insertion site (Fig. 9) (166, 167). The transposon ends are brought into close juxtaposition with each other at the donor site for a coupled reaction that cleaves the transposon termini, introduces a staggered cleavage at the target site, and transfers the 3' ends of the transposon to the overhanging 5' ends at the target (168, 169). The gapped duplexes at the two element ends are then repaired to generate the target site duplication, whose length is a TE family characteristic determined by the transposase. Subsequent excision of the transposon generally leaves behind an imperfect version of the target site duplication, generating sequence diversity (170, 171).

In both bacteria and plants, recognition and cleavage of the two hemimethylated terminal inverted repeats of a single transposon ensures genome integrity and confines transposition to just one of the two newly replicated daughter strands or sister chromatids (36, 172). But like other aspects of transposition, recombination, and DNA repair, this process is error-prone and can be fooled by such transposition events as the insertion of one *Ds* transposon in inverted orientation into the center of itself, giving the chromosome-breaking double *Ds* transposon that led McClintock to her momentous discoveries about how transposons move and restructure chromosomes (173, 174). The bottom line for genomes is that the cleavage and resection of DNA by transposases virtually guarantees sequence variation, genome scrambling, and the appearance of transposons at rearrangement breakpoints. Simply put, transposases drive genome evolution.

Genomic Shock and Transgenerational Epigenetic Inheritance

Both unpredictable stresses, such as irradiation, and predictable abiotic stresses, such as heat shock, elicit from genomes a highly programmed response intended to minimize the impact of the stress. McClintock coined the term “genomic shock” to refer to such a response (175). It is by now amply documented that plant transposons are activated in response to a variety of DNA-damaging agents and both biotic and abiotic stresses, as well as pathogen infection and the passage of plant cells through tissue culture (176–181). Other sources of natural chromosomal disturbance are provided by interspecific hybridization and allopolyploidization, both of which trigger the activation of transposons (182–184). This appears to be true as well in other eukaryotes, from yeast to flies to humans. Telomerases are relatives of retrotransposon-encoded reverse transcriptases, and transposons either comprise or can fill in for missing telomeres in flies and yeast, respectively (152, 185–187).

Evidence is accumulating that both biotic and abiotic stresses induce a heritable increase in the ability of plants to withstand infection and tolerate stress (188–191). DNA damage, pathogen infection, and abiotic stresses also increase homologous recombination frequency and chromosomal rearrangements, both somatically and heritably (188, 192–195). Thus, responses to stress—whether from pathogens, environmental extremes, or damage to the genetic apparatus—evoke not just a transcriptional response, but also a profound and to some extent heritable change in the epigenetic framework. Such changes can loosen the epigenetic constraints on transposons, allowing stress-inducible TEs to propagate stress-inducible promoters to other genes through transposition (181).

Just as McClintock reported that broken chromosome ends can “heal,” so do transposition bursts subside, over both short and long runs (175). Some of the *Arabidopsis* transposons and retrotransposons demethylated in a genetic background devoid of the MET1 DNA methylase are gradually remethylated by RNA-dependent DNA methylation within several generations after reintroduction of a wild-type MET1 gene (196–198).

Heat-induced transcription and transposition of the *Arabidopsis* *ONSEN* retrotransposon is rapidly silenced, becoming transgenerational only in plants with a compromised RdDM pathway (181). Thus, transcriptional activation by demethylation can also trigger a feedback mechanism that restores methylation and resiles transposons. Recent years have seen progress in identifying the components of the restructuring response, but we do not yet know how cells and organisms perceive and initiate epigenetic reorganization in response to either genetic disruptions or environmental stressors.

Evolvability and Its Agents

I have argued that epigenetic mechanisms not only underpin the management of transcription and chromosome structure, but also provide the key to understanding the size and organization of eukaryotic genomes.

Plant responses to stress—whether from pathogens, environmental extremes, or damage to the genetic apparatus—evoke not just a transcriptional response, but also a profound and to some extent heritable change in the epigenetic framework.

They assure the stability of chromosomes, including vast menageries of TEs, and manage the replication and segregation of the genetic material in both mitosis and meiosis. My argument is that TEs accumulate because of, not despite, the epigenetic mechanisms that control homology-dependent recombination,

whose dominance keeps the genomes of prokaryotes and many lower eukaryotes small. Absent the existence of such mechanisms, ectopic, homology-dependent recombination among dispersed TEs would rapidly eliminate them, either directly by intrachromosomal deletions or indirectly by creating nonviable chromosomes.

But although epigenetic mechanisms slow the pace of genome restructuring to an evolutionary time scale, the impact of transposons and retrotransposons on genes and genomes is inescapable. Indeed, their ability to move and to move sequences has shaped higher eukaryotic genomes, from the structuring and restructuring of genes and their regulatory sequences to the shaping and reshaping of the genomic landscape. It is becoming increasingly difficult to escape the conclusion that eukaryotic genome evolution is driven from within not just by the

gentle breeze of the genetic mechanisms that replicate and repair DNA, but by the stronger winds (with perhaps occasional gale-force gusts) of transposon activity. The ability to evoke rapid genome restructuring is at the heart of eukaryotic evolvability—the capacity of organisms with larger and larger genomes to maintain evolutionary flexibility.

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Nina V. Fedoroff

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