Mobile DNA II
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Chapter 50

Miniature Inverted-Repeat Transposable Elements and Their Relationship to Established DNA Transposons

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THE DISCOVERY OF MITEs IN PLANT AND ANIMAL GENOMES

A 128-bp insertion in a mutant maize *waxy* gene (the *wxB2* allele) led to the identification of a group of related elements called *Tourist* in the untranslated regions of genes from diverse grass species (5, 7). A 257-bp insertion in a sorghum *Tourist* element led to the discovery of a second family of elements, called *Stowaway,* in the genes of a diversity of flowering plants (6). *Tourist* and *Stowaway* elements share structural but not sequence similarity. Both are short (~100 to 500 bp), have conserved terminal repeats, have target site preference (*Tourist,* TAA; *Stowaway,* TA), and, of most significance for this chapter, have no coding potential.

All of these features are reminiscent of the nonautonomous members of some DNA transposon families. However, it was the high copy number of *Tourist* and *Stowaway* elements and the uniformity of related elements that served to set them apart from previously described nonautonomous elements. For this reason, and because they were being mistakenly classified as SINEs, it was decided to name these and other structurally related elements miniature inverted-repeat transposable elements (MITEs) (4, 64). Although first discovered in plants, MITEs were soon found in several animal genomes, including those of *Caenorhabditis elegans* (41, 42), mosquitoes (16, 58), fish (25), *Xenopus* spp. (62), and humans (38, 51).

With the advent of genome sequencing projects, vast amounts of DNA sequence, from a wide variety of plant and animal species, have become available for analysis. MITEs, with their high copy number, distinct structural features (target site duplications [TSDs] and terminal inverted repeats [TIRs]), and compact stature, are relatively easy to mine from DNA sequence databases. As such, the number of MITEs and MITE families has proliferated in the literature much as the MITEs themselves have proliferated

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in the genome. Initially this led to a confusing jumble of names and hypothesized relationships. This confusion reflected two important facts about MITEs. First, as very short, nonautonomous elements, none of the available MITE sequences revealed clear-cut relationships with known transposases. Second, and perhaps most significantly, no MITE family to date has been shown to be actively transposing. In the absence of coding sequences and activity, it has been difficult to determine how MITEs originate and how they attain their high copy numbers.

Fortunately, this situation has changed dramatically in the past few years as two approaches have been successfully employed to establish relationships between MITEs and existing DNA transposon families. We call these approaches "bottom up" and "top down," and they are illustrated below in the descriptions of Tc1/*mariner*-like MITEs and *PIF/Harbinger*-like MITEs, respectively. With a bottom up approach, the sequences of nonautonomous family members are used as queries to identify potentially autonomous family members through similarities in their TSDs and TIRs. This approach has revealed complex relationships between hundreds of MITE families and the well-characterized Tc1/*mariner* superfamily of transposases. In contrast, the top down approach began with the discovery that a genetically active DNA transposon system in maize (called *P Instability Factor* [*PIF*]) had MITE members (called *miniature PIF* [*mPIF*]) and led to the identification of a new superfamily of transposases that are responsible for the transposition of *Tourist*-like MITEs.

ORGANIZING THE DIVERSITY OF MITEs

The data summarized in Table 1 are the first attempt to classify most or all of the previously published MITEs as well as those recently generated by the systematic mining of the complete genome sequences of *Arabidopsis thaliana* and *C. elegans* (consensus sequences are available through Repbase at http://www.girinst.org [28]). As mentioned above, this task is complicated by the fact that MITEs lack coding capacity and different families generally have common structural characteristics but little if any sequence similarity. In Table 1, MITEs are grouped into superfamilies based on their association with established superfamilies of transposases. The link between a given MITE family and a source of transposase is first based on the length and sequence of the TSD, as this feature is a function of the transposase (chapter 1). This relationship is strengthened when significant sequence similarity, in particular in the TIRs, is shared between MITEs and a transposon(s) with coding capacity for the transposase. We have attempted to quantify these various degrees of association in Table 1 by assigning each match between a MITE family and a potential partner with one of four levels of sequence similarity. These are as follows.

At level 1, the MITE and the DNA transposon share significant sequence similarity over the entire MITE sequence; the MITE is likely to be derived from the larger element by an internal deletion. At level 2, the MITE and DNA transposon share sequence similarity in their terminal and subterminal regions; only an internal segment of the MITE appears unrelated to the partner element. At level 3, the MITE only has the TIRs identical or almost identical to those of a DNA transposon from the same genome. At level 4, the MITE only has the TIRs identical or almost identical to those of a DNA transposon from another species.

A level 1 or 2 designation indicates that there is strong evidence for the involvement of the larger element in both MITE origin and amplification. A level 3 designation indicates strong evidence that the MITE family was mobilized by the transposase encoded by the larger transposon (or by a close relative) but does not provide information as to the origin of the MITE. Finally, a level 4 designation provides only indirect evidence of a possible relationship between a MITE family and an existing superfamily of transposase and thus reflects the most tentative assignment. Evidence supporting the data presented in Table 1 is presented in sections that follow.

THE Tc1/*mariner* SUPERFAMILY AS A SOURCE OF MITEs

As discussed above, *Stowaway* was one of the first described MITE families. Fifty *Stowaway* elements were initially discovered in close association with the genes of diverse flowering plants, including six grass species and 12 species of dicotyledonous plants (6). All *Stowaway* elements described to date have conserved 11-bp termini (5′-CTCCCTCCGTT-3′), are short (70 to 350 bp) and homogeneous in length within subfamilies, and have a preference for insertion into the TA dinucleotide (the TSD) (6, 32, 64). From the initial discovery of *Stowaway* elements, a connection was noted between *Stowaway*'s preference for TA dinucleotide insertion sites and the fact that this feature is also a hallmark of the Tc1/*mariner* superfamily of DNA transposons (6).

MITEs Related to Tc1/*mariner* Transposons in *C. elegans*

More-extensive sequence relationships between MITEs and Tc1/*mariner* elements were first estab-

lished with *C. elegans*, where MITEs make up more than 2% of the genome (42, 54). Using computer-assisted searches, Oosumi et al. (41, 42) identified several MITE families with copy numbers that range from a few dozen (*Cele5*) to several hundred (*Cele2*). Most of the *C. elegans* MITE families share their termini (~20 to 150 bp) and TSD sequence with one of the many Tc1/*mariner* transposons described in this species (including Tc1, Tc2, Tc5, and *mariner*-like elements [MLEs] [see references 41 and 42, Table 1, and chapter 22).

Comparison of the transposase-encoding Tc elements and the numerous MITE families suggested possible scenarios for the origin of MITEs in *C. elegans*. For example, *CeleTc2*, *Cele11*, and *Cele12* all have Tc2-like TIRs, while their internal sequences

Table 1. Classification of MITEs

Possible transposase superfamily	Levels of similarity[a]	Species	Family	Approx. copy no.	TSD[b]	No. of TIRs	Approx. size (bp)	Reference(s)[c]
Tc1/*mariner*								
D39D mariner-like	3	Various flowering plants	*Stowaway*[d]	ND[e]	TA	>10	70–350	6, 11
	2, 3	*Oryza sativa*	Various *Stowaway*[d]	40,000	TA	20–150	100–350	61, b
	4	*Arabidopsis thaliana*	Various *Stowaway*[d]	300	TA	25–100	200–300	32, c
D34D	3	*Caenorhabditis elegans*	*Cele1*	1,000	TA	120	330	41
mariner-like	3	*C. elegans*	*Cele2*	1,500	TA	90	325	41
	3	*C. elegans*	*Cele4*	300	TA	11	470	41
	3	*C. elegans*	*Cele6*	100	TA	50	160	41
	3	*C. elegans*	*PALTA1_CE*	300	TA	580	1,466	a
	3	*C. elegans*	*PALTA2_CE*	50	TA	600	1,534	a
	3	*C. elegans*	*PALTA4_CE*	20	TA	87	198	a
	3	*C. elegans*	*TIR54TA1_CE*	100	TA	54	200	a
mariner-like	4	*Culex pipiens*	*Milord*	3,000	TA	118	521	c
D34D mariner-like	1	*Homo sapiens*	*Mrs/Madel*	2,400	TA	37	80	38
pogo-like	1	*A. thaliana*	*Emigrant*	250	TA	24	550	9
	4	*Aedes aegypti*	*Wujin*	3	TA	23	185	58
	4	*C. pipiens*	*Mimo*	1,000	TA	23	350	16
	4	*C. pipiens*	*Nemo*	ND	TA	25	324	16
	4	*Anopheles gambiae*	*TA-I*	1,840	TA	24	355	56
	4	*A. gambiae*	*TA-II*	1,080	TA	23	368	56
	4	*A. gambiae*	*TA-IV*	130	TA	20	363	56
	4	*A. gambiae*	*TA-V*	300	TA	22	348	56
	1	*Drosophila melanogaster*	*Dm-mPogo*	30–50	TA	25	180	56
	1, 3	*H. sapiens*	MER2 group[d]	50,000	TA	23–25	250–700	51
impala-like	3	*Fusarium oxysporum*	*mimp*	ND	TA	27	~220	22
Tc1-like	3	*C. elegans*	*Cele*Tc1/Tc7	30	TA	60–350	920	a
	3	*C. elegans*	Tc6	30	TA	765	1,600	12
	3	*C. elegans*	*NPALTA1_CE*	50–100	TA	49	173	a
	4	*A. gambiae*	*TA-III*	970	TA	54	245	56
	4	*C. pipiens*	*Mikado*	~1,500	TA	30	830	c
	4	*C. pipiens*	*Mirza*	ND	TA	72	170	c
	4	*Tenebrio molitor*	*DEC*	3,500	TA	26	475	3
Tc2-like	3	*C. elegans*	*Cele11*	25	TA	52	220	42
	3	*C. elegans*	*Cele12*	50	TA	39	370	42
	3	*C. elegans*	*Cele*Tc2	150	TA	111	210	41
	4	*A. aegypti*	*Pony*	15,000	TA	24	500	57
Tc5-like	3	*C. elegans*	*Cele*Tc5	15	TA	280–680	500–1,400	41

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Table 1. *Continued*

Possible transposase superfamily	Levels of similarity[a]	Species	Family	Approx. copy no.	TSD[b]	No. of TIRs	Approx. size (bp)	Reference(s)[c]
PIF/Harbinger	2, 3	Grasses	Various *Tourist*[d]	>5,000	TWA	13–100	100–400	5, 7, 45
	3	*Zea mays*	*Hbr*	4,000	TWW	14	310	67
	3	*Z. mays*	*Zm-mPIF*	6,000	TWA	13	350	68
	3	*Z. mays*	*B2*	1,000	TWA	14	130	7, 27
	3	*O. sativa*	*Castaway*	1,000	TWA	13	350	4
	3	*O. sativa*	*Ditto*	2,000	TWA	15	300	4
	3	*O. sativa*	*Wanderer*	4,000	TWA	10	300	4
	3	*O. sativa*	*Gaijin*	3,000	WWW	17	180	4
	3	*O. sativa*	*Explorer*	2,000	TWA	13	240	4
	2	*O. sativa*	*Os-mPIF2*	150	WWW	14	260	68
	3	*A. thaliana*	*MathE1*	50	TWA	25	400	53
	3	*A. thaliana*	*ATTIRX1*	70	TWA	16–40	350–400	29
	3	*A. thaliana*	*ATTIR16T3A*	100	TWA	16	500	29
	3	*A. thaliana*	Various *Tourist*[d]	>300	TWA	>14	300–500	32
	2	*A. thaliana*	*At-mPIF2*	20	TWA	14	400	68
	4	Bell pepper and Solanaceae	*Alien*	2,400	TWA	25	400	43
	3	*C. elegans*	*Cele7*	300	TWA	170	360	40
	1	*C. elegans*	*PAL3A_CE*	100	TWA	28	150	61, a
	2	*Caenorhabditis briggsae*	*Cb-mPIF1a*	50	TWA	60	244	68
	1	*C. briggsae*	*Cb-mPIF1b*	30	TWA	27	60	58
	4	*A. gambiae*	*Joey*	1,120	TNA	70	350	2, 56
	4	*Anopheles stephensi*	*NOS*	ND	TAA	29	492	34
	4	*A. gambiae*	*TAA-I*	40	TAA	38	184	56
	4	*A. gambiae*	*TAA-II*	320	TAA	26	142	56
	4	*Xenopus laevis*	*Vi*	7,500	TWA	16	100–470	48
piggyBac/TTAA	4	*C. elegans*	*PALTTAA1_CE*	100	TTAA	285	592	a
	4	*C. elegans*	*PALTTAA2_CE*	100	TTAA	65	174	a
	4	*C. elegans*	*PALTTAA3_CE*	50	TTAA	285	594	a
	4	*A. aegypti*	*Wuneng*	2,700	TTAA	19	256	58
	4	*X. laevis*	*REM1*	25,000	TTAA	15	500	19
	4	*Xenopus* spp.	*Xbr*	5×10^3–2×10^4	TTAA	42	475	62
	4	*Xenopus* spp.	*XR*	ND	TTAA	12	500	62
	4	*Xenopus* spp.	*Ub3*	ND	TTAA	44	450	62
	4	*Xenopus* spp.	*Ub7*	20,000	TTAA	22	500	62
	4	*Xenopus* spp.	*Xfb*	ND	TTAA	127	500	62
	4	*Xenopus* spp.	*Pir*	4,000	TTAA	15	500	23
	4	*Danio rerio* and other fish	*Angel*	10^3–10^4	TTAA	26	315	25
	3	*H. sapiens*	MER75	ND	TTAA	14	242/540	d
	3	*H. sapiens*	MER85	2,000	TTAA	13	140	d
hAT	1, 3	*O. sativa*	Various *hAT*-like[d]	2,000	8 bp	12–15	100–600	b
	3	*A. thaliana*	*MathE3*	<100	8 bp	70–135	300–1,200	53
	1, 3	*A. thaliana*	Various *hAT*-like[d]	20–200	8 bp	12–20	250–800	c, e
	4	*A. gambiae*	*Pegasus*	90	8 bp	8	534	2, 56
	4	*A. gambiae*	*8bp-I*	725	8 bp	8	534	56
	3	*X. laevis*	*Ocr*	1×10^3–5×10^3	8 bp	19	300–400	39
	3	*X. laevis*	*Vision*	300	7 bp	14	284	33
	1, 3	*H. sapiens*	MER1 group[d]	100,000	8 bp	14–15	200–500	51

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Table 1. *Continued*

Possible transposase superfamily	Levels of similarity[a]	Species	Family	Approx. copy no.	TSD[b]	No. of TIRs	Approx. size (bp)	Reference(s)[c]
Mutator-like	2, 3	*O. sativa*	Various *Os-mMu*[d]	3,000	9 bp	10–300	100–700	b
	2, 3	*A. thaliana*	Various *At-mMu*[d]	<100	9 bp	~300	1 kb	e
	4	*Medicago truncatulata*	*Bigfoot*	10^3–10^4	9 bp	38	175	10
Mirage	3	*C. elegans*	*PALNN1_CE*	20	2 bp	70	210	a
	3	*C. elegans*	*NPAL0A_CE*	20–30	2 bp	118	286	a
Merlin/*IS1016*	4	*C. elegans*	*PAL8C_CE*	>100	8 bp	50	200–350	a, c
Unclassified (unknown transposase)		*Ipomoea nil*	*MELS3*	ND	3 bp?	50	185	24
		Ipomoea nil	*MELS4*	ND	3 bp?	49	215	24
		Ipomoea nil	*MELS5*	ND	3 bp?	13	251	24
		Ipomoea nil, *Ipomoea purpurea*	*MELS8*	ND	ND	10	355	13
		Neurospora crassa	*Guest*	ND	GTA	15	98	66
		O. sativa	*Snabo-2*	150	4 bp?	107	383	11
		A. aegypti	*Wukong*	2,200–3,000	TAYA	17	430	58
		Ciona intestinalis	*Cimi-1*	17,000	T(A/T)ATA	30	193	49
		A. thaliana	*Hairpin*	10	CTWAR	114	238	1
		X. laevis	*Glider*	20,000	6–11 bp	14	150	33
		C. elegans	*Cele42*	600	6 bp	23	240	54
		C. elegans	*Cele14*	2,000	6 bp	58	180	42
		C. elegans	*PALTTTAAA1_CE*	50	TTTAAA	320	680	a
		C. elegans	*PALTTTAAA2_CE*	50	TTTAAA	320	680	a
		O. sativa	*Snap*	100	7 bp	SIRs[f]	170	52
		O. sativa	*Crackle*	500	8 bp	SIRs	385	52
		O. sativa	*Pop*	50	8 bp	SIRs	125	52
		A. aegypti	*Microuli*	3,000	TTAA	SIRs	209	56
		C. pipiens	*Mint*	ND	CA	SIRs	141	16
		Drosophila obscura group	*SGM-IS*	>100?	ND	SIRs	600–1,200	37

[a]Between MITEs and potential partner DNA transposon (see text for description of each level).
[b]N = any nucleotide; W = A or T; Y = C or T; R = A or G.
[c]a, V. Kapitonov and J. Jurka, Repbase update, *C. elegans* section (http://www.girinst.org); b, N. Jiang, unpublished data; c, C. Feschotte, unpublished data; d, J. Jurka and A. Smit, Repbase update, *H. sapiens* section; e, V. Kapitonov and J. Jurka, Repbase update, *A. thaliana* section.
[d]Refers to several MITE families grouped into the same superfamily based on TIR and TSD sequence similarities.
[e]ND, not determined.
[f]These elements have no TIRs but have subterminal inverted repeats (SIRs).

have little similarity to each other or to other Tc2 sequences (42). To explain this and related instances, the authors hypothesized that a single Tc element type can mobilize a variety of highly divergent sequences. Supporting this notion was the finding that Tc7 MITEs could be mobilized in vivo and in vitro by an autonomous Tc1 element, even though Tc7 and Tc1 share only their 36 terminal nucleotides (44). It is possible that Tc7 was initially derived from a complete Tc1-like element that was subsequently lost from the genome of most *C. elegans* strains (44). Alternatively, new MITEs may arise de novo from the fortuitous association of TIRs flanking unrelated segments of DNA.

MITEs Related to Tc1/*mariner* Transposons in Humans

Examples of Tc1/*mariner*-related MITEs have also been found in the human genome. Several groups independently discovered an abundant family of short (80-bp) palindromic elements, called *Mrs* or *Made1* (38, 40, 51). These elements are extremely homogeneous in length, consisting of two 37-bp TIRs separated

by a 6-bp sequence. The TIRs are 80 to 100% similar to those of MLEs that are dispersed in the genome (38, 40, 51). These were the first MLEs identified in mammals and were subsequently grouped into the *Hsmar1* family (46; also see chapter 48). There are ~200 *Hsmar1* copies in the human genome, while the copy number of the 80-bp *Mrs* MITE is estimated to be ~2,400 (46). Based on their sequence and size homogeneity, it was proposed that *Mrs* MITEs originated from a single *Hsmar1* deletion derivative (38, 46).

The human genome also harbors another large family of MITEs called the MER2 group (51). MER2 elements are short (200 to 800 bp) and form numerous families that are distinguished by their homogeneity of length and sequence, once again hinting that a family originated from a single element (Repbase update, *H. sapiens* section [http://www.girinst.org]). Overall it is estimated that our genome harbors more than 30,000 MER2 MITEs. Based on similar TIR sequences and TA target site duplication, MER2 is associated with larger transposons, called *Tiggers,* that contain large open reading frames (ORFs) with similarity to the *pogo* subgroup of Tc1/*mariner* transposases (51; also see chapter 48). *Tigger* subfamilies can be directly connected with MER2 subfamilies by sequence similarity that extends into internal regions. For example, MER28 MITEs (~435 bp) resemble internal deletion derivatives of *Tigger2,* but they are five times more abundant than *Tigger2* (~5,000 versus 1,000 copies [51]).

MITEs Related to Tc1/*mariner* Transposons in Insects

MITEs with TIRs that are strikingly similar to those of *pogo*-like elements have been described in three distantly related species of mosquitoes (16, 56, 58) and fragments of *pogo*-like transposases have been detected in the mosquito *Anopheles gambiae* (http://bioweb.pasteur.fr/BBMI/trans.html; C. Feschotte, unpublished data). It is thus likely that *pogo*-like transposases are also responsible for the proliferation of multiple MITE families in mosquitoes. The original *pogo* element from *Drosophila melanogaster* has also given rise to a homogeneous group of deletion derivatives (180 bp [60]) that could be viewed as one of the rare MITE families in this species (with ~40 copies in the available genomic sequence). Finally, another abundant MITE family, *Pony* (~18,000 copies), from the genome of the mosquito *Aedes aegypti,* displays TIRs with striking similarity to those of the Tc2 transposon from *C. elegans* and also has the TA target site duplication (57). Thus, *Pony* MITEs may have proliferated by using endogenous Tc2-like transposases. Taken together, these data suggest that Tc1/*mariner* transposons have been a common source of transposase for the origin and/or amplification of MITEs in animals.

MITEs Related to Tc1/*mariner* Transposons in Plants

Tc1/*mariner* transposons were long believed to be absent or rare in the plant kingdom (8, 20). However, recent studies indicate that Tc1/*mariner* transposons are actually widespread in plant genomes and have probably given rise to a large fraction of plant MITEs (15, 17). Evidence connecting a plant MITE family with a Tc1/*mariner* transposon was first obtained by analyzing the genome sequence of *Arabidopsis.* Homology-based searches revealed that *Emigrant,* the first MITE family identified in this species (9), originated from the larger *Lemi1,* which has coding capacity for a *pogo*-like transposase (15, 29). *Lemi1* is present as a single copy in the Columbia ecotype, where there are ~250 copies of *Emigrant.* Sequence similarity between *Emigrant* and *Lemi1* is moderate (~70%) but encompasses the entire MITE consensus sequence (15). Therefore, *Emigrant* MITEs probably originated by internal deletion of *Lemi1* or from a closely related element.

To date, plant MITEs related to *pogo*-like transposons have only been identified in *Arabidopsis* (15, 29). However, there are now several lines of evidence that the widespread *Stowaway* MITEs are related to a new group of Tc1/*mariner* transposons. That *Stowaway* MITEs display a strong preference for TA targets was the first indication that this heterogeneous group might be related to the Tc1/*mariner* superfamily (6). Recently it was shown that the 10 terminal nucleotides characteristic of *Stowaway* MITEs match those of the two elements identified in soybean and rice that possess long ORFs with similarity to animal *mariner* transposases (26, 55, 61). This provides additional evidence that *Stowaway* MITEs were mobilized by transposases encoded in *trans* by MLEs.

Given the wide distribution of *Stowaway* in plants, it follows that MLEs should also be widespread in their genomes. Database searches and a PCR approach exploiting newly designed plant-specific primers were recently combined to demonstrate that MLEs are present in a wide range of flowering plants (17). Phylogenetic analyses of over 100 plant MLE transposase sequences revealed the existence of multiple and divergent lineages of MLE transposases (17). Together these results provide an explanation for the proliferation, diversity, and success of *Stowaway* MITEs in plant genomes.

Tourist-LIKE MITEs ARE RELATED TO MEMBERS OF THE *PIF/Harbinger* SUPERFAMILY

Connections between several families of MITEs and the Tc1/*mariner* superfamily of transposases are numerous and widespread in animal genomes and now also in plant genomes. In contrast, connections between the large numbers of *Tourist*-like MITEs and possible sources of transposase were much more elusive because *Tourist* TSDs and TIRs were not related to any well-characterized transposon family (7).

This situation began to change with the discovery of *Harbinger*, a 5.4-kb element that was mined from the *Arabidopsis* genome sequence (29). *Harbinger* contains an ORF that could potentially encode a transposase related to transposases from bacterial insertion elements of the IS*5* group (29, 32; also see chapter 15). Similarities between *Harbinger* and two diverse nonautonomous transposons in *C. elegans*, *Turmoil1* and *Turmoil2*, were also noted (29). These elements all have similar 3-bp TSDs and TIRs. Further analysis of *Turmoil* family members revealed their relationship with *Tourist*-like MITEs (31).

Maize *PIF* and *mPIF* MITEs

The relationships between *Harbinger*, *Turmoil*, and *Tourist* MITEs reflect the association of a putative transposase from one kingdom with MITEs in another kingdom. Based on the four levels of confidence used in Table 1, this evidence would be classified as level 4. Thus, additional evidence was needed to bolster the ties between transposase source and MITEs. This could be the identification of transposase-encoding elements and related MITEs in the same genome or the identification of additional and possibly active elements related to the *Harbinger* family. Fortunately, the *PIF* transposon system of maize provided the additional evidence needed to unequivocally associate a transposase source with *Tourist*-like MITEs.

PIF is an active DNA element family first discovered as multiple mutagenic insertions into the maize *R* gene (63). Additional *PIF* elements were later isolated and characterized, including a putative autonomous element, *PIFa*, which has coding sequences related to *Harbinger*, *Turmoil*, and distantly to bacterial IS*5* elements (68). The ~25 *PIF* elements in the maize genome have 14-bp TIRs and are flanked by the 3-bp TTA TSDs. Of particular interest was the finding that *PIF* is associated with a maize *Tourist*-like MITE named *mPIF*. There are many similarities between *PIF* and *mPIF* (Fig. 1) (68). First, they share identical 14-bp TIRs and similar subterminal sequences (~70% over ~100 bp at each end). In fact, the discovery of the large *mPIF* family was due to its sequence similarities to *PIF*. In addition, they both insert preferentially into the 9-bp imperfect palindrome CWCTTAGWG (W stands for either A or T), and insertion leads to duplication of the central TTA. While the extent of sequence similarity alone indicates that *mPIF* was probably derived from *PIF* or from a closely related element, their identical, extended target sites provide the strongest evidence that both elements were mobilized by the same or a related transposase (68).

PIF-Like Elements and Their MITEs in Other Organisms

The discovery of *PIF* led to the recognition of a new superfamily, *PIF/Harbinger*, with members identified thus far in plants (maize, rice, and *Arabidopsis*), nematodes (*C. elegans* and *Caenorhabditis briggsae*), and a fungus (*Fusarium neoformans*). All elements encode a putative transposase with 45 to 65% amino acid identity that is also distantly related to bacterial IS*5* transposases (30, 68). Like the maize *PIF*, these *PIF*-like elements also have TIRs and TSDs that are similar to those of *Tourist*-like MITEs. In fact, once *PIF*-like elements were uncovered in the genomic sequences of rice, *Arabidopsis*, and *C. briggsae*, it was not difficult to identify their associated *Tourist*-like MITEs (Fig. 1). For example, the rice *Os-PIF2* element is associated with a MITE family called *Os-mPIF2*. Sequence similarity between *Os-PIF2* and *Os-mPIF2* encompasses the entire *Os-mPIF2* length (70 to 90% overall), and a deletion breakpoint can be clearly defined (Fig. 1). Another example is the association between the *Arabidopsis At-PIF2* element and *At-mPIF2*. These elements even share an identical mismatch in their imperfect TIRs. Finally, the *PIF*-like element in *C. briggsae*, *Cb-PIF1*, is associated with two MITE families, the longer *Cb-mPIF1a* and the shorter *Cb-mPIF1b*. As with *Os-PIF2* and *Os-mPIF2*, a clear deletion breakpoint can be defined both within *Cb-PIF1* and *Cb-mPIF1a* (Fig. 1).

OTHER MITEs AND NONAUTONOMOUS DNA TRANSPOSONS

Other MITEs

Table 1 summarizes the evidence that most of the MITE families described to date can be assigned to one of two superfamilies, Tc1/*mariner* and *PIF/Har-*

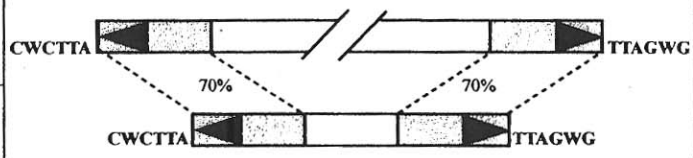
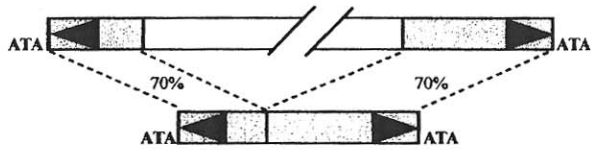
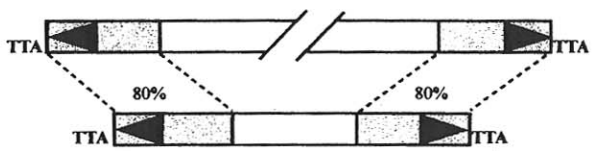
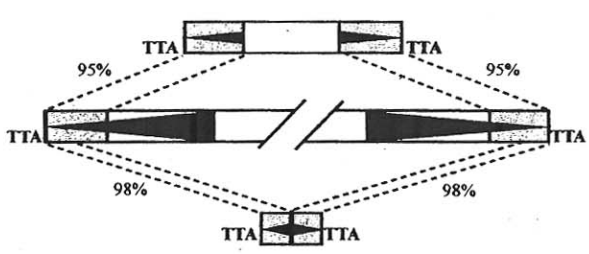
Name	Comparison between *PIFs* and *mPIFs*	Size (bp)	Copy No.	*mPIF* Similarity
Zm-PIFa		3,728	1	—
Zm-mPIF		358	~6,000	90-95%
Os-PIF2		3,770	ND	—
Os-mPIF2		270	~150	70-90%
At-PIF2		4,229	1	—
At-mPIF2		410	~20	91-98%
Cb-PIF1		~2,000	<10	—
Cb-mPIF1a		244	~50	85-91%
Cb-mPIF1b		60	~30	99-100%

Figure 1. Similarities between *PIF*-like elements and *Tourist*-like MITEs. Grey rectangles represent regions conserved between *PIF* elements and related *mPIF* MITES (nucleotide homology shown in percentage). Black triangles represent element TIRs.

binger. Analysis of large data sets of genome sequences harboring a vast number of MITEs, such as those of *C. elegans, Arabidopsis,* or *Oryza sativa,* has confirmed that most MITE families are related to these two superfamilies of transposases. However, in addition to these associations, a survey of mined MITEs from the rapidly expanding rice database indicates that the remaining rice MITEs are most likely to be derived from other DNA transposon superfamilies such as *hAT* (*Ac*-like) or *Mutator* (Table 1 and chapters 23 and 24). Although poorly represented among the MITEs identified so far in *Arabidopsis,* rice, and other grasses, *hAT*- and *Mutator*-related MITEs might be abundant in other plant species. For example, *Bigfoot* MITEs in the *Medicago* genus (alfalfa) are present at 10^3 to 10^4 copies per genome, and they share several structural features reminiscent of *Mutator*-like transposons such as a 9-bp TSD (10).

The large vertebrate genomes, such as those of *Xenopus,* fish, and humans, also harbor several MITE families that are probably unrelated to the two superfamilies. One group is referred to as the TTAA (or T2) superfamily and is characterized by TTAA target site duplications and a particular sequence motif in the TIRs (62). Several TTAA MITE families were identified in *Xenopus* (62), fish (25), and more recently *C. briggsae* (Feschotte, unpublished data), *C. elegans,* and humans (Repbase update [http://www.girinst.org]). Although no related elements with coding capacity for a transposase have as yet been identified in these species (except perhaps in humans; see below), the TTAA target preference may suggest a link with a newly recognized superfamily of DNA transposons called *piggyBac* (chapter 48). The founding member of this superfamily is an autonomous transposon, *piggyBac,* from the lepidopteran *Tri-*

choplusia ni (18). The *piggyBac* transposase is responsible for the specific integration into TTAA targets (18). Elements with the same target site preference and coding capacity for similar putative transposases have recently been identified in other insects and humans (50; also see chapter 48). Thus, it is tempting to connect the TTAA MITEs from *Xenopus,* fish, and nematodes with the *piggyBac*-like transposases that may reside in their respective genomes.

Finally, *hAT*-related transposases appear to be involved in the propagation of a number of animal MITEs. In humans, the MER1 group of MITEs are flanked by an 8-bp TSD and they possess TIRs similar (or identical) to those of *hAT* transposon fossils present in the same genome (50, 51). Based on similarities in TIRs and TSDs, a relationship to *hAT*-like transposons was also proposed for several *Xenopus* and mosquito MITE families (56, 62).

Several MITE families described from plants, animals, and fungi do not share any structural or sequence features with known DNA transposon families. Therefore, their classification and source of transposase remain elusive (Table 1). An intriguing example is *Microuli,* a homogeneous family of elements from the mosquito *A. aegypti* that lack TIRs but have subterminal inverted repeats (59). Elements similar in structure but not in sequence have been found in rice and in other dipteran species (4, 16, 37) (Table 1). Along with their subterminal inverted repeats, the fact that they exhibit a preference for insertion into targets of conserved length (and sequence in the case of *Microuli*) suggests that they are nonautonomous DNA elements mobilized by transposases encoded in *trans* (59).

Helitrons: Rolling-Circle Transposons in Eukaryotes

An even more puzzling group of nonautonomous transposons, designated *Helitron* transposons, was recently identified in the *A. thaliana, C. elegans,* and rice genomes (29, 32, 53, 61). Unlike MITEs, these elements have no inverted repeats and do not generate TSDs but have conserved ends and form homogeneous subfamilies with relatively high copy numbers (~2% of their genomes). It was only when the complete genome sequence of *Arabidopsis* became available that the autonomous partners could be identified, leading to the discovery of a new type of eukaryotic DNA transposons (30). Autonomous *Helitron* transposons were subsequently identified in *C. elegans,* and both autonomous and nonautonomous forms were found in the rice genome (30). The autonomous *Helitron* transposons are large elements (5.5 to 15 kb) with coding capacity for a product sharing similarities to DNA helicases and to the replicator initiator proteins of rolling-circle plasmids and certain single-stranded DNA viruses (see chapter 37). Along with other structural characteristics, these features suggest that *Helitron* transposons define a new type of transposable elements employing a rolling-circle mode of transposition (30; also see chapter 37).

A MODEL FOR THE ORIGIN OF MITEs

MITEs were discovered only 10 years ago. Until very recently, investigators wondered whether they were class 1 or class 2 elements and, if they were class 2 elements, how they were able to attain such high copy numbers. From the summary presented in this chapter, it is now evident that MITEs are nonautonomous DNA elements that originated from a subset of the existing DNA transposons. One hallmark of these transposons appears to be target site preference. Whether all DNA transposons are able to give rise to MITEs remains an open question.

The issue of MITE copy number has become more complex. The high copy numbers attributed to many MITE families may, in the majority of instances, result from independent amplifications of subfamilies in the same genome. This is illustrated best in rice, where *Stowaway* MITEs account for over 2% of genomic DNA (35). However, upon closer inspection it can be seen that there are over 30 subfamilies of *Stowaway* MITEs and none of these have attained copy numbers significantly greater than 1,000 (N. Jiang, C. Feschotte, and S. R. Wessler, unpublished data). In contrast, larger genomes (such as maize, human, and *Xenopus*) harbor very-high-copy-number MITE families. For example, there are over 6,000 copies of *mPIF* in maize that appear to have arisen from a single ancestral element (Fig. 1) (68).

A model for the origin and amplification of MITEs, based largely on the data summarized in this review, is shown in Fig. 2. According to this model, a MITE family is composed of MITE subfamilies that have arisen from related autonomous elements in a single genome. A single type of autonomous element can give rise to one or multiple MITE families or can activate nonautonomous elements derived from a related autonomous element (if, for example, that autonomous element has become inactive or is no longer in the genome). Another aspect of this model is that MITEs originate from autonomous elements like previously described (conventional) nonautonomous elements. This may result from an abortive gap repair mechanism following transposition or another transposase-dependent deletion event, such as those described for the *Drosophila P* element or the *Ac/Ds,*

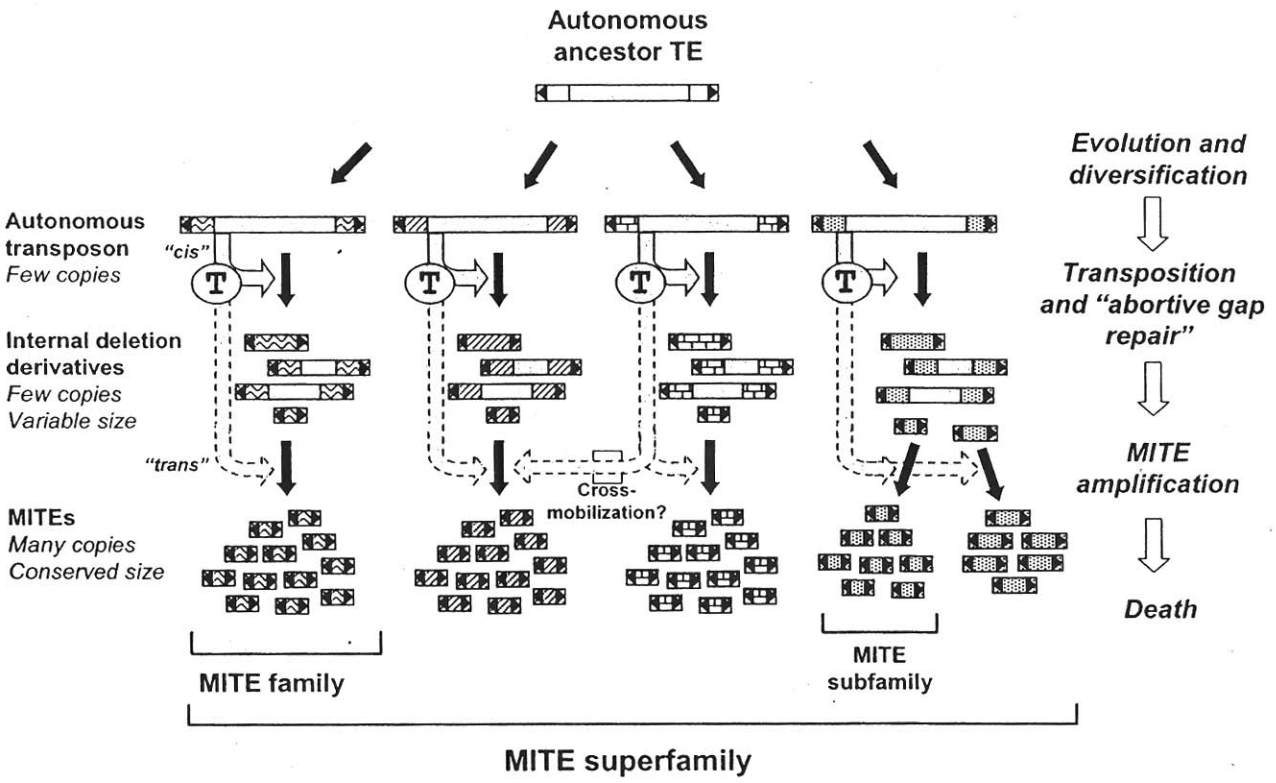


Figure 2. Model for the origin and amplification of MITEs. See text for discussion. The circled T stands for the transposase. Transposase is known to mediate the formation of nonautonomous derivatives through mechanisms such as abortive gap repair (grey arrows) (14, 21, 47, 65). The subsequent amplification of one or a few deletion derivatives (i.e., MITE amplification [dashed grey arrows]) is likely to be mediated by the same transposase or those produced by a close relative (trans- or cross-mobilization, respectively). The different patterns at the ends of the autonomous elements represent different subterminal sequences with identical or near-identical TIRs (black triangles).

Mutator, and *En/Spm* systems of maize (14, 21, 36, 47, 65; also see chapters 21 and 24). However, MITE derivatives are proposed to possess some feature(s) that allows them to be subsequently amplified to higher copy numbers than their sibling conventional nonautonomous elements (Fig. 2). Testing this aspect of the model will require in vivo and in vitro systems in which the requirements for MITE transposition can be assessed. This should now be possible since active transposases that are related to those involved in the amplification of MITEs are now available.

The final aspect of the model involves the possible impact of MITE amplification on the evolution of autonomous elements. The proliferation of nonautonomous elements has been hypothesized to lead to the extinction of the cognate autonomous element through titration of active transposase (20). In this regard, the birth and explosive amplification of MITEs could paradoxically be a death sentence for the transposase and consequently for the whole subfamily. However, selection would then lead to the diversification of the transposase by favoring variants with altered binding sites, thus ushering in a new cycle of birth and death.

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