Transposons in *C. elegans**

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Abstract

Transposons are discrete segments of DNA capable of moving through the genome of their host via an RNA intermediate in the case of class I retrotransposon or via a "cut-and-paste" mechanism for class II DNA transposons. Since transposons take advantage of their host's cellular machinery to proliferate in the genome and enter new hosts, transposable elements can be viewed as parasitic or "selfish DNA". However, transposons may have been beneficial for their hosts as genome evolution drivers, thus providing an example of molecular mutualism. Interactions between transposon and *C. elegans* research were undoubtedly mutualistic, leading to the advent of needed genomic tools to drive *C. elegans* research while providing insights into the transposition field. Tc1, the first *C. elegans* transposon to be identified, turned out to be the founding member of a widespread family of mobile elements: the Tc1/*mariner* superfamily. The investigation into transposition regulation in *C. elegans* has uncovered an unforeseen link between transposition, genome surveillance and RNA interference. Conversely, transposons were utilized soon after their identification to inactivate and clone genes, providing some of the first molecular identities of *C. elegans* genes. Recent results suggest that transposons might provide a means to engineer site-directed mutations into the *C. elegans* genome. This article describes the different transposons present in the *C. elegans* genome with a specific

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emphasis on the ones that proved to be mobile under laboratory conditions. Mechanisms and control of transposition are discussed briefly. Some tools based on the use of transposons for *C. elegans* research are presented at the end of this review.

1. *C. elegans* transposons, the catalog

Analysis of the *C. elegans* genome sequence indicates that approximately 12 % of the *C. elegans* genome is derived from transposable elements (*C. elegans* Sequencing Consortium, 1998; Sijen and Plasterk, 2003; Stein et al., 2003). However, most of these sequences are fossil remnants that are no longer mobile but can be used by molecular archeologists to trace back the interactions between parasitic "selfish DNA" (Orgel and Crick, 1980) and a host genome (for review see Brookfield, 2005; Kazazian, 2004). In this section, I will mostly describe elements that can transpose under laboratory conditions (Figure 1). Other elements will be mentioned only briefly.

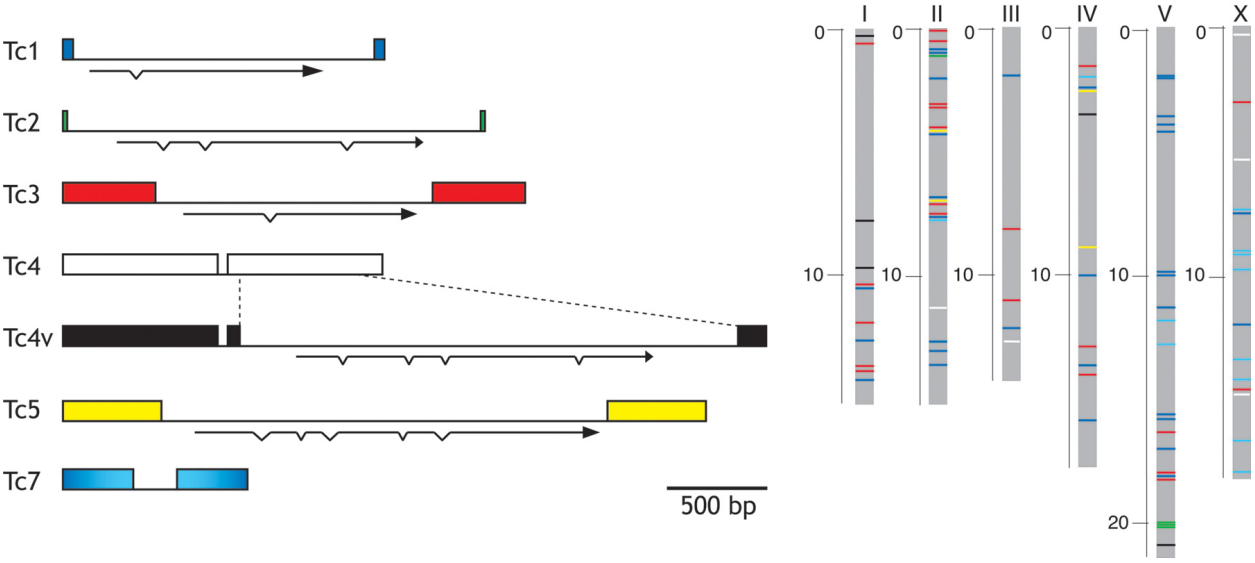

Figure 1. Active transposons in *C. elegans*. The structure of the transposons that proved to be mobile are depicted in the left panel. They all are class II DNA tranposons flanked by Terminal Inverted Repeats (boxes) and containing one open reading frame (arrows) encoding the transposase enzyme. Distribution of the different transposons in the genome of the *C. elegans* Bristol N2 strain is represented in the right panel using the same color code as on the right (Tc7 are in light blue; however, as represented on the left panel, 36 of the 38 outer bp of Tc7 are identical to the one of Tc1) The sizes of the chromosomes are in Mb. Reprinted from Fischer et al. (2003). Copyright © 2003 the Genetics Society of America.

1.1. The Tc1 and Tc3 transposons

Tc1 and Tc3 are the most active and best characterized transposons in *C. elegans*. The article of Anderson, Emmons and Moerman (1992) describes how circulating information between laboratories conducting simultaneous molecular and genetics approaches lead to the identification of the first transposable element in *C. elegans*, Tc1. Tc1 was isolated as a repeated sequence responsible for polymorphism among different strains (Emmons et al., 1983; Liao et al., 1983; Rosenzweig et al., 1983). Analysis of spontaneous and reversible mutations of the myosin heavy-chain *unc-54* demonstrated the mobile nature of Tc1 (Eide and Anderson, 1985; Eide and Anderson, 1988). This feature was used to clone another muscle gene *unc-22* by transposon tagging (Moerman et al., 1986; Moerman and Waterston, 1984). The subsequent characterization of additional spontaneous *unc-22* mutations lead to the identification of Tc3 (Collins et al., 1989).

Tc1 is 1,610 bp long and contains two 54-bp terminal inverted repeats (TIRs; Rosenzweig et al., 1983). Tc3 is an element of 2,335 bp with 462 bp TIRs. The genome of the Bristol N2 strain contains 31 and 22 copies of Tc1 and Tc3, respectively (Fischer et al., 2003). These numbers are strain dependent. In some strain isolates such as Bergerac, Tc1 transposition is active in the germ line and each haploid genome contains up to 300-500 Tc1 copies (Egilmez et al., 1995; Emmons et al., 1983; Liao et al., 1983).

Tc1 and Tc3 are part of a superfamily of transposable elements which is named after its two best-studied members: Tc1 and the related transposon *mariner* which was identified in 1986 in *Drosophila mauritiana* (Jacobson et al., 1986). Tc1/*mariner* elements are probably the most widespread DNA transposons in nature and can be found in fungi, plants, ciliates and animals including ecdysozoans and vertebrates (for review see Plasterk et al., 1999).

These transposons are about 1,300-2,400 bp in length, are flanked at either end by TIR and contain a single open reading frame that encodes a transposase enzyme. Tc1/*mariner* transposases all contain a triad of acidic residues (DDE or DDD) with a characteristic spacing which is shared by a superfamily of endonucleases (review in Haren et al., 1999, see below). Primary sequence conservation of the Tc1/*mariner* transposases is relatively low (about 15 % identity among the superfamily) but phylogenetic analysis suggests that all Tc1/*mariner* were derived from a common ancestor and might all transpose through similar mechanisms.

1.2. Other active transposons

The Tc2 element was initially identified as a polymorphism marker (Levitt and Emmons, 1989). It is 2,074 bp in length and has perfect terminal inverted repeats of 24 bp (Ruvolo et al., 1992). There are 4 full-length Tc2 copies in the N2 genome, each flanked by a TA dinucleotide at either end. In addition, up to 300 copies of remnant Tc2 elements have been detected in the genome (Duret et al., 2000). Although not tested experimentally, gene prediction algorithms suggest that Tc2 encodes a 477 aa protein containing a DNA binding domain and a catalytic domain related to the DDE endonuclease superfamily. Transposition of Tc2 has been documented in the offspring of interstrain crosses between Bristol N2 and Bergerac BO or in a *mut-2* background (Francis et al., 1995; Levitt and Emmons, 1989).

The first Tc4 element was identified as a mutagenic insertion in the gene *unc-86* (Yuan et al., 1991). It is a fold-back element of 1.6 kb which contains almost perfect terminal inverted repeats of 774 bp with a 57-bp unique internal sequence. No open reading frame can be detected within Tc4. Five such Tc4 copies are present in N2 Bristol. A variant class of Tc4 (Tc4v, 5 copies in the N2 genome) contains a 2,343 bp sequence which replaces 477 bp in one of the inverted repeats (Li and Shaw, 1993). A transcript from Tc4v has been detected. It may encode a 537-aa protein which resembles transposases of the DDE superfamily. Tc4v might provide in *trans* the transposase required to mobilize all Tc4 elements. These elements duplicate a 3-bp target sequence TNA upon integration and are mobile in *mut-2* (Yuan et al., 1991) and *mut-7* (Ketting et al., 1999) *mutator* (*mut*) backgrounds.

The Tc5 element is present in four copies per haploid genome (Collins and Anderson, 1994). It is 3,171 bp long and has 491 bp long terminal inverted repeats. Tc5 and Tc4v share common features. Tc5 encodes a putative 532 amino acid transposase which is overall 33 % identical to the Tc4v transposase, Tc4 and Tc5 TIRs share a few short nucleotide sequences, and integration of Tc5 causes duplication of the same TNA trinucleotide sequence. Tc5 elements are mobile only in *mut-2* (Collins and Anderson, 1994) and *mut-7* (Ketting et al., 1999) backgrounds.

Tc7 is a 921 bp element that uses the Tc1A transposase for transposition (Rezsohazy et al., 1997). It is made up of two 345 bp inverted repeats separated by a unique sequence that does not contain an ORF. 36 of the 38 outer bp of Tc7 are identical to the ones of Tc1. Forced expression of Tc1A in somatic cells causes transposition of Tc7. Furthermore, Tc7 is mobile in the germ line in the same backgrounds as Tc1 such as *mut-6* and *mut-7* lines.

CemaT1 elements were identified in a genome search as a clade of transposons intermediate between *mariner* and Tc1 (Claudianos et al., 2002). They are 1,281 bp long and are flanked by two perfect 26 bp inverted repeats. 12 copies are present per haploid genome, of which 8 contain a single ORF encoding a putative 336 amino acid transposase. These elements can be excised in somatic cells and might possibly transpose in the germ line of TR403 strains (Brownlie and Whyard, 2004).

1.3. Transposons with no detected activity:

The genome of *C. elegans* contains several class II transposons that are not mobile under laboratory conditions. Tc3-CeIIa and CeIIb are closely related to Tc3 (Tu and Shao, 2002), Tc6 is a fold-back element (Dreyfus and Emmons, 1991; Dreyfus and Gelfand, 1999), Tc8 is related to the plant Tourist transposon (Le et al., 2001), Tc9 and Tc10 are related to Tc4(v) (Fischer et al., 2003), and the *mariner*-like element *mle-1* is more closely related to the fly *mariner* elements than to the *C. elegans* Tc1 (Robertson and Lampe, 1995; Sedensky et al., 1994). In addition, up to 2 % of the *C. elegans* genome is made up from MITEs (miniature inverted-repeat transposable elements). MITEs are small non-autonomous elements that derive from transposons and are identified based on the presence of target site duplications and terminal inverted repeats (Oosumi et al., 1995; Oosumi et al., 1996; Surzycki and Belknap, 2000).

The genome of *C. elegans* also contains class I retrotransposons. These elements are subclassified into Long Terminal Repeat (LTR) retrotransposons that resemble retroviruses but usually lack the gene encoding the envelop protein and non-LTR retrotransposons. 124 sequences derived from *Cer* LTR retrotransposons, including 20

full-length elements, have been identified in the genome sequence of N2 (Bowen and McDonald, 1999; Britten, 1995; Frame et al., 2001; Ganko et al., 2001). They can be grouped in 19 families related either to the *gypsy* or *Bel* clades of retrotransposons. These LTR retrotransposons constitute 0.4 % of the *C. elegans* genome (Ganko et al., 2003). A thousand sequences derived from non-LTR retrotransposons can be detected in the genome and grouped into the 4 families: *Rte* (Youngman et al., 1996), *NeSL* (Malik and Eickbush, 2000), *Sam* and *Frodo* (Marin et al., 1998). These elements only constitute 0.2 % of the *C. elegans* genome (Zagrobelny et al., 2004) suggesting that retrotransposons have been altogether strongly counterselected in this compact genome as compared to other species such as *Homo sapiens* in which more than 40 % of the genome is composed of retroelement sequences. The *C. elegans* genome contains full length LTR and non-LTR elements but no retrotransposition events have been documented so far under laboratory conditions.

2. Mechanisms of Tc1 and Tc3 transposition

Tc1/*mariner* transposons move via a "cut-and-paste" mechanism: transposase binds the TIRs, catalyses excision and subsequent reinsertion into target DNA in a TA dinucleotide and leaves behind a double-strand DNA break which is repaired by the cellular machinery.

The Tc1A transposase is the only factor required in trans to mediate Tc1 transposition: forced expression of Tc1A in Bristol N2 enhances somatic transposition of Tc1 (Vos et al., 1993) and recombinant transposase purified from *E. coli* is capable of performing the entire transposition reaction *in vitro* (Vos et al., 1996). Similar evidence has been obtained for the Tc3A transposase (van Luenen et al., 1993; van Luenen et al., 1994). The Tc1A and Tc3A transposases are 343 and 329 acid long, respectively. They contain a bipartite N-terminal DNA-binding domain similar to the paired domains found in some transcription factors (van Pouderoyen et al., 1997; Watkins et al., 2004). This domain binds in a sequence-specific manner to bases located at the terminal part of the inverted repeats (position 7 to 26 in Tc1; Colloms et al., 1994; Vos and Plasterk, 1994; Vos et al., 1993). A non-specific DNA-binding domain located in more C-terminal regions of the transposase might interact with the first four bases of the TIR and the flanking TA dinucleotide, thus bringing the catalytic domain of the transposase in close proximity to the cleavage site.

Tc1A and Tc3A share a common catalytic triad of acidic residues with transposases and integrases and also with more distant enzymes that promote phosphoryltransfer reactions such as RNaseH (for review, see Haren et al., 1999). In these proteins the D,DX35E motif (two aspartates and a glutamate 35 residues away) was shown to be part of a catalytic pocket in which the acidic residues coordinate one or two magnesium or manganese ions that play a key role during transesterification reactions. Mutation of any of the DDE residues in Tc1A or Tc3A inactivate the transposase activity (van Luenen et al., 1994; Vos and Plasterk, 1994). Terminal inverted repeats are necessary and sufficient *in vitro* and *in vivo* for transposition as long as transposase is provided in *trans*. Within the TIRs, the first four bases of the transposon and the transposase binding sites located immediately downstream are strictly required for excision (van Luenen et al., 1994; Vos and Plasterk, 1994). However, an element only containing the 26 terminal nucleotides of Tc1 is mobilized *in vitro* ten times less efficiently than an element with full length TIRs (Vos et al., 1996), suggesting that the transposase binding sites contained in this terminal fragment are not sufficient for fully efficient transposition. First, additional internal sequence might be required in *cis*. Second, the distance between the two TIRs might be important since insertion of foreign DNA into Tc1 causes an exponential decrease of transposition frequency (Fischer et al., 1999). A similar phenomenon has been described in related transposons such as *Sleeping Beauty* (Izsvak et al., 2000), *Himar1* (Lampe et al., 1998) and *Mos1* (Lohe and Hartl, 2002) but its molecular basis is not known.

Transposon excision results from a pair of double-strand breaks at the ends of the inverted repeats (Figure 2). Coordination of cleavage at the ends of a transposon is presumably mediated by the formation of a "synaptic complex" in which the two transposon ends on the same molecule are brought together via transposase-mediated oligomerization. In Tc1 and Tc3, the 5' end is cleaved two bases from the end of the transposon and the 3' cut occurs at the junction of the transposon with the flanking DNA, resulting in a two-base pair 3'-hydroxyl overhang at each termini. Following excision, the transposon then integrates 5' of a thymidine nucleotide at a TA target sequence using the free 3' hydroxyl as a nucleophile. Repair of the resulting single-strand gaps causes a duplication of the TA dinucleotide at each transposon end. In vitro experiments demonstrated that the transposase was sufficient to catalyze excision and insertion reactions (Lampe et al., 1996; Tosi and Beverley, 2000; Vos et al., 1996). However, Tc1/*mariner* transposases can interact with cellular factors such as the DNA-bending protein HMGB1 which might affect the efficiency of transposition *in vivo* (Zayed et al., 2003).

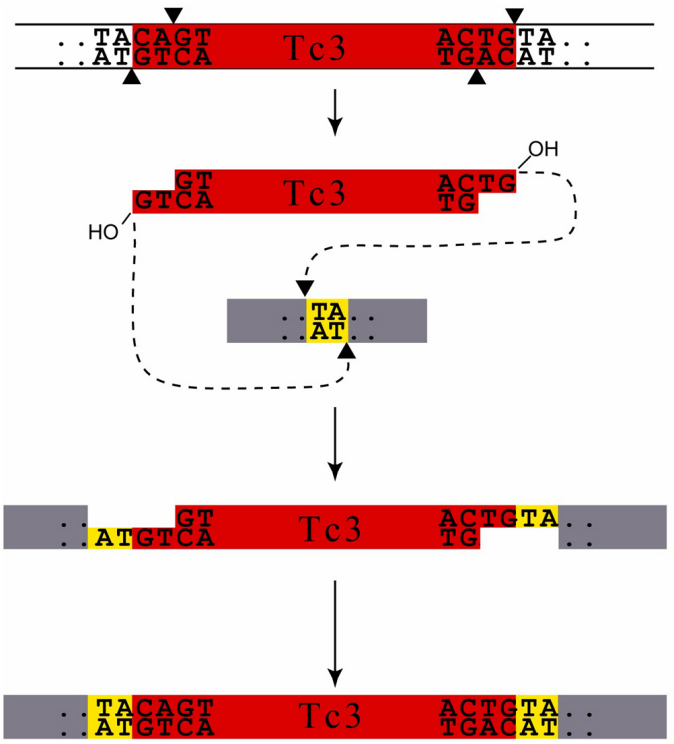

Figure 2. Mechanism of Tc3 transposition. Tc3, a member of the Tc1/mariner transposon superfamily, is mobilized by a "cut-and-paste" mechanism. The transposase excises the transposon by causing double-strand breaks at the end of the transposon (arrow heads). The DNA cut is staggered, resulting in a two-base pair 3'-hydroxyl overhang at each termini. Following excision, transposons then integrates 5' of a thymidine nucleotide at a TA target sequence using the free 3' hydroxyl as a nucleophile. Repair of the resulting single-strand gaps causes a duplication of the TA dinucleotide at each transposon end. Adapted from van Luenen et al., 1994.

3. Transposon insertion target

Tc1, Tc3 and Tc7 always integrate into the TA sequence and Tc4 and Tc5 integrate into TNA sites. Since intron sequences are AT-rich, this may explain why such elements have a higher probability of inserting into introns rather than into coding sequences (Martin et al., 2002). However, all TA dinucleotides do not represent equivalent targets. First, the difference between insertion "hot spots" and "cold spots" depends on the target sequence since *in vitro* transposition using naked DNA and purified Tc1A transposase mostly recapitulates Tc1 insertion preferences (Ketting et al., 1997; Vos et al., 1996). The comparison of Tc1 and Tc3 insertion sites reveals a weak consensus limited to 4 nucleotides on each side suggesting that the transposase interacts directly with the TA dinucleotide and less specifically with surrounding bases. Second, there are regional differences in insertion preferences. For example, the gene *unc-22* is hit about a 100 times more frequently than *unc-54* although its coding sequence is only 3.5 times larger (Eide and Anderson, 1985; Moerman and Waterston, 1984). Part of these differences might arise from the fact that transposons such as Tc1 have a preference for local reinsertion into the same chromosome from which they were excised (Fischer et al., 2003). However, *Mos1*, a *drosophila* transposon from the Tc1/*mariner* family was recently mobilized in *C. elegans* from an extrachromosomal array (Bessereau et al., 2001). Analysis of random insertions indicates the presence of a 4 kb hot-spot at the right end of chromosome I which cannot be explained by local transposition (Granger et al., 2004). Third, transposon sequences are not evenly distributed in the genome and a correlation has been observed between the density of DNA transposons but not retrotransposons and the regions of higher chromosomal recombination rate (Duret et al., 2000; Rizzon et al., 2003). Whether these two features are mechanistically linked or indirectly reflect another parameter such as differences in chromatin structure remains to be established.

4. Repair of the excision site

Upon excision, Tc1/*mariner* transposons leave behind a DNA double strand break. Such breaks are repaired by the cellular machinery using two general types of repair: non homologous end joining (NHEJ) and repair by homologous recombination (for a review on DSB repair, see Haber, 2000; Figure 3). The decision to use one or

another mechanism depends on tissue type and cell-cycle stage. During NHEJ, DNA ends are joined after little or no trimming. Since Tc1 and Tc3 excision leaves behind the duplicated TA and non complementary two nucleotide 5' overhangs, NHEJ generates short footprints ranging from 4 base pair insertion with TA duplications to a few base pair deletion. Occasionally, wild type sequence can be regenerated at the site of excision. NHEJ is active in *C. elegans* somatic cells but is also used in the germ line (Eide and Anderson, 1988; Emmons and Yesner, 1984; Emmons et al., 1983; Plasterk, 1991; Ruan and Emmons, 1987; van Luenen et al., 1994).

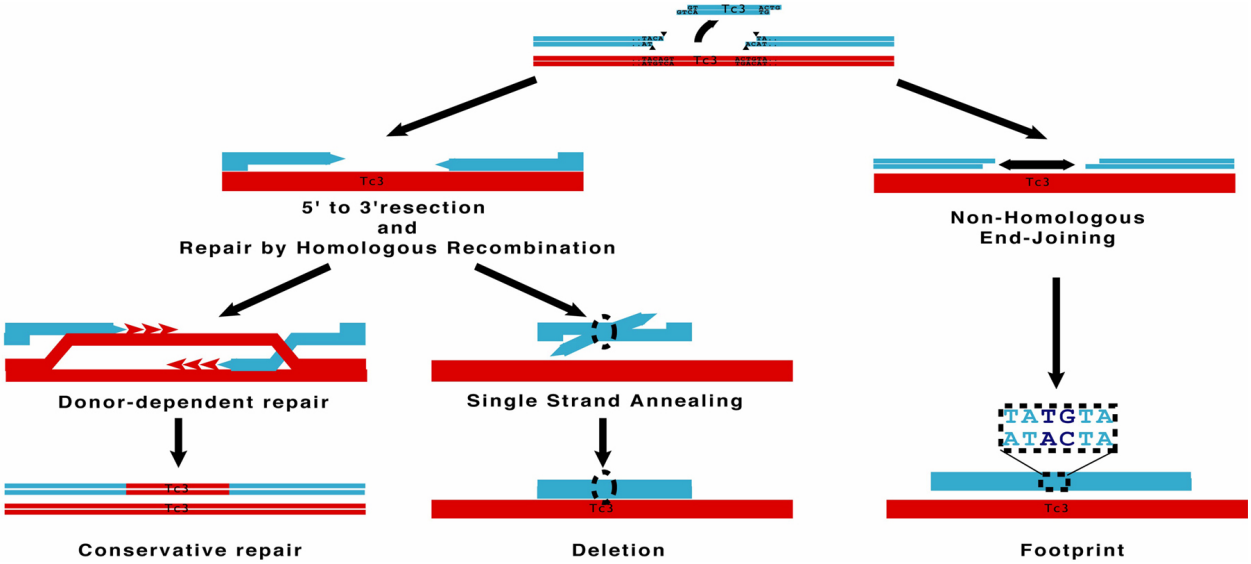

Figure 3. Repair at the excision site. Excision of a Tc1/mariner transposon generates a double-strand break in the chromosome *(blue)*. In this example, the homologous chromosome *(red)* is homozygous for the Tc insertion. The double-strand break is repaired by the cellular machinery using different possible pathways. Ends can be resected, resulting in 3' single-stranded ends that can engage a recombination process. If the homologous chromosome (or the sister chromatid) is used as a template, the repair process regenerates an intact copy of the transposon at the site of excision *(left panel)*. If resection exposes complementary strands of homologous sequences on the same chromosome *(dotted ellipse)*, repair can occur by single-strand annealing and generates variable deletions of the sequence flanking the site of excision *(middle panel)*. Alternatively, repair can be achieved by non-homologous end-joining (NHEJ)*(right panel)*. In that case, ends are processed and repair leaves short footprints *(dotted rectangle)*. For Tc1 and Tc3, one of the most common footprints contain two nucleotides from the transposon end *(dark blue)* and the duplicated TA.

DSB repair by homologous recombination first involves the 5' to 3' resection of the DSB ends to produce long 3'-ended single-stranded DNA tails. Several pathways can be used for repair that will generate different class of final products. In some cases, resection exposes complementary sequences allowing single-strand annealing and subsequent deletion of the segments located between these sequences. Such deletions were noticed in revertants of an *unc-22* Tc1 reversion allele (Kiff et al., 1988). Zwaal et al. (Zwaal et al., 1993) demonstrated that such deletions could be isolated among the progeny of most Tc1 mutants and could be used in a reverse genetic approach to generate deletion alleles in genes of interest. Alternatively, recombination can occur with the sister chromatid or the homologous chromosome. This latter mechanism seems preferentially used for Tc1 repair in the germ line. If the animal is heterozygous for the Tc1 insertion, gene conversion will revert the broken locus to wild-type. If the animal is homozygous for the Tc1 insertion, repair will regenerate a Tc1 insertion at the excision site (Plasterk, 1991). Interestingly, analysis of Tc1 sequence polymorphisms suggest that the repair machinery can switch from allelic Tc1 template to Tc1 elements located elsewhere in the genome, resulting in chimeric Tc1 elements (Fischer et al., 2003). Occasionally, repair can be imperfect and generate partial deletions of the transposon (Fischer et al., 2003; Lohe et al., 2000).

5. Regulation of transposition

All *C. elegans* strains contain numerous transposons prone to be mobilized. However, in most strains such as the reference isolate Bristol N2, transposition is only detected in somatic cells but is completely silenced in the germ line (Emmons and Yesner, 1984). In some natural isolates such as the strain Bergerac BO which was isolated in Bergerac, France (Nigon and Dougherty, 1949), Tc1 transposons are active in the germ line (Egilmez et al., 1995; Eide and Anderson, 1985; Greenwald, 1985; Moerman et al., 1986). Bergerac individuals exhibit a mutator phenotype due to spontaneous mutations caused by *de novo* Tc1 insertions. Strikingly, EMS-induced mutations of single loci such as *mut-2* (Collins et al., 1987) or *mut-7* (Ketting et al., 1999; Tabara et al., 1999) are able to globally activate the transposition of multiple Tc families including Tc1, Tc3, Tc4 and Tc5. Therefore, the germ line of *C.*

elegans is permissive for transposition but a defense-mechanism exists to protect the genome from heritable defects caused by transposon jumps.

Transposition silencing in the germ line involves an RNA interference (RNAi)-related mechanism. This notion emerged after the realization that a set of mutants including *rde-2/mut-8*, *rde-3/mut-2*, *mut-7*, *-14*, *-15* and *-16* are defective for both RNAi and germ-line silencing of transposition (Chen et al., 2005; Collins et al., 1987; Ketting et al., 1999; Tabara et al., 1999; Tijsterman et al., 2002; Tops et al., 2005; Vastenhouw et al., 2003; for a complete review, see Vastenhouw and Plasterk, 2004). In a simplified model of RNAi, a double-stranded RNA (dsRNA) molecule is cleaved into 21-24 nucleotide-long short-interfering RNAs (siRNAs) by the RNAse III-like enzyme DCR-1 of the dicer family. siRNAs are loaded into the RNA-induced silencing complex (RISC) and used for specific cleavage of target RNAs. dsRNAs derived from Tc1, Tc3 and Tc5 Terminal Inverted Repeats are indeed detected in Bristol N2 animals that might arise from the fold-back of transcripts encompassing entire Tc elements. siRNAs corresponding to Tc1 and other transposons are produced in the N2 strain (Ambros et al., 2003; Sijen and Plasterk, 2003). These siRNAs seem to be functional in the germ line since a Tc1 TIR fused to gfp causes silencing of GFP expression, at least in part, by post-transcriptional silencing of the transgene in the germ line (Sijen and Plasterk, 2003). Therefore, in a simple model, RNAi might repress transposition by causing the degradation of tranposon-derived mRNA in the germ line, hence preventing the expression of any Tc transposase. In other tissues, transposon-induced RNAi might be less efficient, hence enabling somatic excision. However, mutator strains exist that are not RNAi deficient. In *mut-4*, *-5* and *-6* mutant backgrounds, transposition of Tc1 but not of other Tcs is specifically derepressed (Mori et al., 1988). These loci have not been identified at the molecular level but they have been proposed to correspond to specific Tc1 copies. For example, truncated Tc1 elements might produce transcripts which lack a sequence targeted by the RNAi surveillance system but could still produce a functional transposase. Alternatively, these elements might be full-length Tc1 elements inserted in genomic regions that lead to very efficient transcription of these copies in the germ line, hence allowing some transcripts to escape degradation. In addition to Tc1-specific mutators, a number of genes are required for global silencing of transposition but not for RNAi (Ketting et al., 1999; Vastenhouw et al., 2003). It is not clear at the moment if these genes act in a specific branch of an RNAi-dependent process or if they are involved in an RNAi-independent control of transposition.

6. Transposon-based tools for *C. elegans* research

6.1. Gene identification in forward genetic screens

Insertional mutagenesis with transposons generates mutant alleles that are tagged by the presence of a transposon. This molecular tag can subsequently be used to identify the mutated gene. Mutator strains and Tc1 gene tagging was used early in forward genetic screens to identify mutated-genes before the genome project reagents were available (Greenwald, 1985; Moerman et al., 1986) (for review see Anderson, 1995; Plasterk and van Luenen, 1997). Nowadays, Tc elements can be used in combination with PCR to amplify the genomic sequence that flank a mutagenic insertion and identify the mutated gene without genetic mapping (Wicks et al., 2000). However, using Tc elements as mutagens has some major drawbacks. First, the mobilization of Tc transposons is not restricted to a single class of elements in mutator strains. Second, there are several copies of each transposons in the genome which complicate the identification of the mutagenic insertion. Third, in the mutator strains that are used, transposition is not controlled. Some Tc insertions are poorly mutagenic either because they are in introns, or because they are removed from the mature mRNA by aberrant splicing (Rushforth and Anderson, 1996; Rushforth et al., 1993). Spontaneous re-excision can generate mutagenic footprints that generate a stronger phenotype but can no longer be detected in a transposon tagging strategy. These limitations have been circumvented by mobilizing the Mos1 transposon in the germ line of *C. elegans* (Bessereau et al., 2001). *Mos1* is a member of the Tc1/*mariner* family and was isolated from *Drosophila mauritiana* (Jacobson et al., 1986). The *Mos1* element is absent from the *C. elegans* genome and controlled mobilization of *Mos1* is achieved by conditional expression of the *Mos1* transposase. *Mos1* mutagenesis is 10 times less efficient than chemical mutagens but the cloning of mutated genes is extremely fast since *Mos1* insertions represent rare tags that are easy to localize in the genome (Gally et al., 2004; Williams et al., 2005).

6.2. Targeted gene inactivation

Tc1 can be used to target the inactivation of a selected gene. In such approaches, Tc1 are mobilized randomly in a mutator background and independent lines are subsequently screened by PCR for the presence of a Tc1 insertion in the gene of interest (Rushforth et al., 1993). Then, deletions can be generated at low frequency by imprecise repair of double-strand breaks caused by Tc1 re-excision. The line containing the Tc1 insertion in the gene to inactivate is propagated in a mutator background. PCR analysis of the progeny can identify animals that

have lost that Tc1 insertion plus a variable amount of flanking DNA (Zwaal et al., 1993). This strategy has been widely used initially, but more recent protocols of gene inactivation utilize chemical mutagens to generate random deletions in the *C. elegans* genome (Jansen et al., 1997). However, transposon targeted gene inactivation can still be useful when these other strategies fail or if a transposon has already been identified in the gene to inactivate (Korswagen et al., 1996; Martin et al., 2002).

6.3. Site-directed mutagenesis

Gene targeting techniques based on homologous recombination, such as those used in mice and yeast, are difficult in *C. elegans* (Berezikov et al., 2004; Broverman et al., 1993). Transposons might represent an interesting alternative to engineer specific mutations in the genome. In 1992, Plasterk and Groenen (Plasterk and Groenen, 1992) demonstrated that a transgene containing a fragment of the *unc-22* gene could be used as a template to repair a double-strand break caused by Tc1 excision out of the *unc-22* locus in a *mut-6* background (Plasterk and Groenen, 1992). Point mutations contained in the transgene were copied in the genome during the repair process. Therefore, transgene-instructed gene conversion provides a strategy to engineer mutations or introduce exogenous sequence in the genome. However, such events were rare (2.10-5 event per meiosis), thus preventing this technique from being widely utilized in *C. elegans*. Recently, a similar strategy was tried in different mutator backgrounds to engineer deletions and introduce GFP in the genome (Barrett et al., 2004). Transgene-instructed gene conversion was found to be 10 times more frequent than previously reported, thus providing an efficient technique to engineer custom alleles in a reverse genetic approach. Efforts to generate libraries containing transposon insertions in most *C. elegans* genes would expand the use of this method (Granger et al., 2004; Martin et al., 2002).

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