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REVIEW

What makes transposable elements move in the *Drosophila* genome?

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Transposable elements (TEs), by their capacity of moving and inducing mutations in the genome, are considered important drivers of species evolution. The successful invasions of TEs in genomes, despite their mutational properties, are an apparent paradox. TEs' transposition is usually strongly regulated to low value, but in some cases these elements can also show high transposition rates, which has been associated sometimes to changes in environmental conditions. It is evident that factors susceptible to induce transpositions in natural populations contribute to TE perpetuation. Different factors were proposed as causative agents of TE mobilization in a wide range of organisms: biotic and abiotic stresses, inter- and intraspecific crosses and populational factors. However, there is no clear evidence of the factors capable of inducing TE mobilization in *Drosophila*, and data on laboratory stocks show contradictory results. The aim of this review is to have an update critical revision about mechanisms promoting transposition of TEs in *Drosophila*, and to provide to the readers a global vision of the dynamics of these genomic elements in the *Drosophila* genome.
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INTRODUCTION

Transposable elements (TEs) are DNA sequences that are able to move in the genome. The constant appearance of new sequenced genomes reveals that they are major components of the genome of almost all organisms: 12% in *Drosophila*, 45% in humans, 50% in maize and almost 90% in some plants (Flavell, 1986; SanMiguel *et al*., 1996; Kidwell and Lish, 1997; Bennetzen, 2000). In *Drosophila*, TEs are responsible for approximately 80% of phenotypic spontaneous mutations (Green, 1988; Ashburner *et al*., 2005). In humans, the proportion of mutations induced by long interspersed elements represents about 0.17% (Kidwell and Lish, 2002). This proportion is surprisingly low given the high abundance of these sequences in human genome (45%) and reveals that the amount of TEs is not related to the activity. Barbara McClintock in the early 1980s proposed that TEs could be activated by a genomic shock, and this might have an adaptive value on the host genome. For a long time, they were considered as enigmatic sequences with an uncertain role in the genome. However, our comprehension of the impact of TEs on genomes, populations and species adaptation has improved owing to the enormous advances made this past 5 years with accumulating genomics data and a better understanding of epigenetic systems of TE regulation. One major unresolved point, however, is the real mechanism contributing to the activation of the TE transposition in eukaryotes. Activations of TEs by biotic and abiotic stresses and environmental changes have been documented in eukaryotes and plants (Liu *et al*., 1995; Mhiri *et al*., 1997; Walbot, 1999; Bouvet *et al*., 2008). In the case of *Drosophila*, there have been several attempts of demonstrating activation of TEs associated to temperature. Although experiments on transcription rates of some TEs seem to demonstrate a response to thermal gradients (Strand and McDonald, 1985), there is not a consensus relative to variations in transposition rates under thermal stresses (Junakovic *et al*., 1986; Ratner *et al*., 1992; Arnault *et al*., 1997). Although spontaneous mobilizations of TEs in laboratory lines may occur 'spontaneously' without any evident explanation (Gerasimova *et al*., 1985; Biémont *et al*., 1987), dysgenic crosses (Picard, 1976; Kidwell *et al*., 1977; Petrov *et al*., 1995), hybrid crosses (Evgen'ev *et al*., 1982; Labrador and Fontdevila, 1994; Labrador *et al*., 1999) and colonization events (Wisotzkey *et al*., 1997; Labrador *et al*., 1998; Vieira, 1999; García Guerreiro and Fontdevila, 2001; García Guerreiro *et al*., 2008) can greatly increase transposition rates of some TEs.

In *Drosophila*, the detection of transposition associated to different stresses is not easy owing to the difficulties of detecting residual polymorphisms. Moreover, the most widely used techniques as *in situ* hybridization cannot detect transposition in regions close to the original copy, or transpositions inside other elements from the same family. Nowadays, the use of sequencing techniques allows a more accurate comparison of global genomes. Also, the increasing knowledge of the host regulatory mechanisms of transposition indicates the existence of a control that keeps sleeping TEs in the genome, contributing to their persistence. This review relies on *Drosophila* case transposition studies and provides an overview on the current state of knowledge.

SPONTANEOUS TRANSPOSITIONS AND TRANSPOSITION BURSTS

In spite of their ubiquity, TEs move only sporadically in eukaryote genomes (Fedreroff, 2002) due probably to the own host gene and TE regulatory mechanisms. Usually TE transposition rates in natural and

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Table 1 Examples of spontaneous transposition bursts in *Drosophila* species

Spontaneous transpositions	*Strain type*	*Species*	*Elements*
Gerasimova *et al*. (1985)	Laboratory	*D. melanogaster*	*mdg1, mdg2, mdg3, copia, FB,P*
Biémont *et al*. (1987)	Inbred	*D. melanogaster*	*copia*
Pasyukova and Nuzhdin (1993)	Isogenic line	*D. melanogaster*	*copia and Doc*
Biémont *et al*. (1990)	Inbred	*D. melanogaster*	*P*
Biémont *et al*. (1994)	Natural population	*D. melanogaster*	*mdg3*
Yang *et al*. (2006)	Laboratory (*D. yakuba* sequenced genome)	*D. yakuba*	*DINE-1*
Díaz-González *et al*. (2011)	Isogenic lines	*D. melanogaster*	*roo*

laboratory *Drosophila* populations are low, ranging from 10^{-4} to 10^{-6} transposition events per copy, per generation, in laboratory lines and natural populations (Eggleston *et al*., 1988; Harada *et al*., 1990; Nuzdhin and Mackay, 1995; Domínguez and Albornoz, 1996; Vieira and Biémont, 1997; Maside *et al*., 2000, 2001). In spite of their apparent stability, episodes of spontaneous transposition bursts have been detected in prokaryotes (Kocíncová *et al*., 2008) and *Drosophila* (Gerasimova *et al*., 1985; Biémont *et al*., 1987, 1990) without an evident cause (see Table 1). Comparative data of sequenced genomes of *Drosophila melanogaster* and *D. yakuba* species suggest a transposition burst of the DINE-1 retrotransposon in *D. yakuba* genome (Yang *et al*., 2006). In the same way, in *D. simulans*, transposition bursts of *412* element seem to be responsible for the increase of *412* copy number in a natural population from Canberra (Vieira and Biémont, 1997). In most cases, transposition bursts in *Drosophila* occur only in a few individuals and include one or several TEs. The exact mechanisms promoting transposition bursts are at present completely unknown, although these reshuffling events followed by calm periods could constitute an important way in which to promote new genetic variability in *Drosophila* favoring population adaptation and ultimately promoting processes of speciation. TE transposition bursts concomitant with species radiation period were proposed in salmonids, mice and apes (see Rebollo *et al*., 2010), suggesting that these elements could have contributed to the speciation process. However, it is necessary to be cautious because we do not know if transposition bursts and species diversification time coincide exactly. In the case of *Drosophila*, no data of association between transposition bursts and species radiation have been reported. Nevertheless, studies in insects showed that clades that have been increasing in diversity up to the present have significantly smaller genomes than groups in which diversity has remained constant or has decreased (Kraaijeveld, 2010). Independently of these particular considerations, today we cannot deny that transposition events could contribute to the reproductive isolation, the formation of new species (Rebollo *et al*., 2010) and the increase of genome size (Kidwell, 2002; Biémont, 2010).

Environmental stress

Environmental stresses have been found as important factors associated to the TEs' mobilization; experiments on this matter are summarized in Table 2. Abiotic (irradiation, temperature) and biotic (culture tissues or infections by viruses or pathogens) stresses awakened quiescent TEs in plants (Grandbastien, 1998, 2005), yeasts (Staleva and Venkov, 2001) and *Drosophila* (Arnault and Dufournel, 1994; Capy *et al*., 2000). Whereas there is a quasi-unanimous opinion about increases of transposition associated to abiotic and biotic stresses in plants, it is not the case in *Drosophila*, as detailed below.

Abiotic stresses

For a long time, researchers conducted experiments in *Drosophila* in a desperate attempt to mobilize TEs by thermal shock. The experiments that concluded to an effect of heat shock on TEs mobilization in *D. melanogaster* have led to ambiguous data. An absence of mobilization was observed in some cases (Arnault and Dufournel, 1994; Arnault *et al*., 1997) and an increase of transposition in others (Junakovic *et al*., 1986; Ratner *et al*., 1992). These incongruities could be due to the differences in the genetic background of the *Drosophila* stocks used, the type of element considered in each case or both. They could be due also to the difficulty to discern between transpositions '*de novo*' and pre-existing ones. One clear example are the experiments of Ratner *et al*. (1992) and Arnault *et al*. (1997), where both the stressful conditions and the element (*412*) were identical. In the first case, an increase of *412* transposition is observed, but not in the second case. The most striking result is that most *412* new sites detected by Ratner *et al*. (1992) in the F1 of independent treated males were common. We would expect the same result if the control line presented a residual polymorphism of TE insertions, as many time observed in inbred lines, which are sometimes less homozygous than expected even after many rounds of sib matings. The effect of the temperature could be therefore not to increase the transpositions rate, but to select some pre-existing polymorphic sites. However, in this case these intriguing results cannot be attributed, in principle, to pre-existing polymorphic sites because control and experimental samples are descendants of the same male. We have to take into account that detection of transposition in *Drosophila* is not an easy task and that the choice of a very stable control line is critical. Therefore, we are confronted with another question: Is a high stable control line adequate to detect transpositional effects of heat shocks? The answer is not easy in view of the scarce experimental data, the different origin of stocks used and the variety of TEs studied. On the other hand, we do not know exactly how to extrapolate these laboratory conditions to what is really happening in nature, or how temperature is affecting natural populations. Some populational data suggest a correlation between TE copy number and temperature in *D. simulans* for mariner and *412* elements (Chakrani *et al*., 1993; Vieira and Biémont, 1996). Vieira *et al*. (1998) found a lack of association between the copy number of the *roo* element and environmental factors, but a negative correlation of *412* copy number with minimum temperature. Regulatory factors, independent of temperature and acting in *trans*, have been suggested as possible candidates in *412* copy number regulation. The different mechanisms of TE regulation in natural populations could be important in the differentiation of populations, but the effect of environmental factors in these regulatory mechanisms is still unknown.

Temperature stresses are not the only factors associated to transposition. For example, chemical agents were associated to transposition

Table 2 Effects of abiotic and biotic stress on the behavior of *Drosophila* transposable elements

Type of stress	*Effect*	*Elements*	References
Temperature			
Heat shocks	Transcription activation	*copia*	Strand and McDonald (1985)
	Transposition activation	*copia-like*	Junakovic *et al*. (1986)
	No effect on transposition	*copia-like, I, P*	Arnault and Biémont (1989)
	No effect on transposition	*copia-like*	Arnault *et al*. (1991)
	Transposition activation	*412*	Ratner *et al*. (1992)
	No effect on transposition	*copia-like, I*	Arnault *et al*. (1997)
	Transposition activation	*copia-like*	Vasilyeva *et al*. (1999)
	Transposition activation	*copia-like*	Zabanov *et al*. (1990)
Heat and cold shock	Transposition activation	*412*	Bubenshchikova *et al*. (2002)
Extreme temperature	No effect on transposition		Alonso-González *et al*. (2006)
	No effect on transposition	*roo*	Vázquez *et al*. (2007)
Radiation			
X	Transposition activation	*P*	Eeken and Sobels (1986)
γ	No effect on transposition	*hobo*	Zakharenko *et al*. (2006)
γ	Transposition activation	*412*	Zabanov *et al*. (1995)
Chemical			
EMS, MMS, ENU	No excision in gene white	*B104 (roo)*	Soriano *et al*. (1998)
EMS, MMS	Transposition activation	*P*	Blount *et al*. (1985)
ENU	No excision in gene white	*copia*	Baldrich *et al*. (2003)
Ethanol	Transposition activation	*412*	Vasilyeva *et al*. (2003)
Dichlorvos, ecdysterone, H_2O_2	No effect on transposition	*copia-like*	Arnault *et al*. (1991)
Cell cultures	Transposition activation	*copia-like*	Potter *et al*. (1979)
	Transposition activation	*copia-like*	Junakovic *et al*. (1988)
	Transposition activation	*copia-like*	Di Franco *et al*. (1992)
	No effect on transposition	*B104, G, blood*	Di Franco *et al*. (1992)
	Transposition activation	*1731*	Maisonhaute *et al*. (2007)
Viral injection	Somatic transposition	*mdg1*	Jouan-Dufournel *et al*. (1996)
	No effect on transposition	*copia*	Jouan-Dufournel *et al*. (1996)
	Transposition activation	*mdg2*	Nabirochkin *et al*. (1998)
	Excision	*gypsy*	Nabirochkin *et al*. (1998)
	No effect on transposition	*mdg1*	Nabirochkin *et al*. (1998)

Abbreviations: EMS, ethyl methane-sulfonate; ENU, *N*-ethyl-*N*-nitrosourea; H_2O_2, hydrogen peroxide; MMS, methyl methane-sulfonate.

induction in nematodes, yeasts and fungi (Collins *et al*., 1987; Ikeda *et al*., 2001; Staleva and Venkov, 2001). In *Drosophila*, the alkylating agents such as ethyl methane-sulfonate and methyl-methane sulfonate activated the transposition of *P* element (Blount *et al*., 1985). Different doses of ethanol fumes induced the transposition of *412* element in an isogenic strain of *D. melanogaster* (Vasilyeva *et al*., 2003). However, a lack of excision or transposition induced by other treatments has also been reported. For example, Arnault *et al*. (1991) do not detect activation of *copia*-like elements after treatment with dichlorvos, hydrogen peroxide or ecdysone. Similar results were obtained by Soriano *et al*. (1998) and Baldrich *et al*. (2003), where no excision of the TEs' *B104* (*roo*) and *copia* was observed in *Drosophila white* mutants after treatment with different mutagenic agents.

Studies on the effects of radiations on transposition gave different pictures. For example, whereas γ-radiation has no effect on prokaryote transposition (Kupelian and DuBow, 1986), high doses of ultraviolet caused excision in *Escherichia coli* (Eichenbaum and Livneh, 1998) and maize (Walbot, 1999). For *Drosophila*, the radiation effects on transposition are variable and depend on the radiation type and the TEs' studied. For example, X-radiation was associated to *P* element transposition activation (Eeken and Sobels, 1986; Margulies and Griffith, 1991). However, γ-radiation induces transposition of *412* retrotransposon (Zabanov *et al*., 1995), but not of *hobo* (Zakharenko *et al*., 2006) in *D. melanogaster*. It is known that radiations can induce double-strand DNA breakage, leading to a reorganization of the genetic material. On the other hand, it was suggested that ionizing effects of radiations were associated to increases of recombination frequencies (Zakharenko *et al*., 2006). TE insertion location can be affected by these phenomena, and new positions detected could result from the chromosomal changes and not from new transpositions. This could explain why radiation effects were usually associated with the radiation dose applied.

Biotic stresses

Biotic stresses were associated to TEs' mobilization, for example, pathogen attacks activate transposition in plants (Grandbastien,

1998; Beguiristain *et al*., 2001), and tissue cultures have been shown to promote activation of retrotransposons in tobacco (Hirochika, 1993; Hirochika *et al*., 1996) and *MITE* elements in rice (Kikuchi *et al*., 2003). *Drosophila* data about the effects of biotic factors on TE mobilization are scarce, and a lack of consensus exists about their implication. Jouan-Dufournel *et al.* (1996) showed that the injection of the avian RAV-2 particles in *Drosophila* embryos induced the somatic transposition of *mdg1* element, but not *copia*. Similar experiments performed by Nabirochkin *et al.* (1998) with oncoviral particles revealed an increase of transposition of *mdg2* element, whereas the *mdg1* remained stable. In this case, even if mutations and reversions have been detected, it is difficult to discriminate between mutations associated to TE mobilization from those due to the direct integration of the oncovirus. Hongwei *et al.* (2002) demonstrate that *Drosophila* cells infected with the RNA virus FHV (flock house virus) triggered virus RNA silencing and silencing suppressors essential for infection. A protein coded by this virus suppresses RNA silencing against FHV RNAs, blocking both the cleavage of the virus genome and the incorporation of small interfering RNAs into the RNA silencing complex (Chao *et al*., 2005). Similar results were observed in plant viruses encoding RNA silencing suppressors that disrupt the silencing pathway. Therefore, because retrotransposons have structures close to those of retroviruses, we could imagine a similar system where the viral RNAs suppressed the silencing suppressors of transposition. The regulation system of some retrotransposons might become deregulated, leading to an increase of transposition after a viral injection.

The comparison of the number of copies of retrotransposons in *Drosophila* flies and cell cultures showed a higher copy number in cultured cells compared to *Drosophila* individuals (Potter *et al*., 1979; Junakovic *et al*., 1988). In *Drosophila*, short-term cultured cells promote transposition of the *copia*-like elements *412*, *1731* and *297* (Junakovic *et al*., 1988) and *1731* element (Maisonhaute *et al*., 2007). However, mobilization is not observed in long-term cultured cells (Junakovic *et al*., 1988) or in other experiments where the TE mobilization was only observed for most *copia*-like elements, whereas *B104* (*gypsy*-like), *G* (non-long terminal repeat retrotransposon) and *blood* (*copia*-like) elements remain stable (Di Franco *et al*., 1992). In the case of *1731* mentioned above, all new copies seem to be derived from a unique master copy slightly active in *Drosophila* genome and strongly activated during the establishment of the cell culture. The new copies were inserted in genes that might be involved in the biological and physiological differences observed between the cultured cell lines. Despite these observations, the factors responsible for the TE mobilization in cultured cells are unknown so far and the authors attributed the mobilization events to the medium components used for the culture preparation.

Genomic stresses

A genomic stress is any influence that may disrupt the stability of the genome, for example, by altering its genetic background. Genomic stresses can occur, for example, during crosses between individuals that have high genetic differences. In *Drosophila*, these types of stresses can be produced by crosses between different strains and/or species, and a great number of examples of TE mobilization through genetic crosses have been reported. The most known example is the dysgenesis hybrid phenomenon, which occurs in the progeny that results from interbreeding different *Drosophila* strains (Kidwell *et al*., 1977). The most notable features observed in the dysgenic progeny include sterility, male recombination, mutations, chromosomal aberrations and TE mobilization. In *D. melanogaster*, at least three independent systems of hybrid dysgenesis exist: the P–M system (Kidwell *et al*., 1977), I–R (Picard *et al*., 1978) and H–E (Yannopoulos *et al*., 1987). Each type of hybrid dysgenesis is the result of the mobilization of a unique TE (*P*, *I* or *hobo* element) induced by an imbalance in maternal or paternal elements. In *D. virilis*, four different TEs (*Ulysses*, *Penelope*, *Paris* and *Helena*) have been mobilized by an hybrid dysgenesis process (Petrov *et al*., 1995), which have been demonstrated to be associated to the *Penelope* TE by a mechanism in which mobilization of a single element triggers that of others, perhaps through chromosome breakage or for the supply of the proteins necessary for transposition (Evgen'ev *et al*., 1997)

Not all TE mobilizations are the consequence of dysgenic crosses; other crosses can also induce transpositions in *Drosophila*. In *D. melanogaster*, the stalker element has been mobilized after crosses between two different mutant strains (Georgiev *et al*., 1990). Changes in the chromosomal insertion pattern of the *copia* element have been observed during the process of making chromosomes homozygous by the use of balancer chromosomes (García Guerreiro and Biémont, 1995). Higher degrees of heterogeneity in insertion sites of different *copia*-like elements were observed in crosses involving laboratory or wild lines and some balancer stocks (Pasyukova *et al*., 1988; Pasyukova and Nuzhdin, 1993). The most plausible hypothesis to explain these results is to consider that TE mobilization is induced by the crosses used. The genetic background of the stocks involved could have an influence on TE activity via RNA interference pathways as explained below.

All the above-mentioned cases of transposition refer to intraspecific crosses, but interspecific hybridization may also contribute to genetic instability and TE transposition. Well-documented cases of TE transposition activation in interspecific hybrids have been reported in different genera of plants (Liu and Wendel, 2000; Kashkush *et al*., 2002; Josefsson *et al*., 2006; Ungerer *et al*., 2006; Michalak, 2010). Interspecific hybrids in kangaroos induce TE activation and centromeric expansion (O'Neill *et al*., 1998; Metcalfe *et al*., 2007). In *Drosophila*, crosses between *D. buzzatii* and *D. koepferae* induce the transposition of *Osvaldo* retrotransposon in hybrids (Labrador *et al*., 1999), and crosses between *D. virilis* and *D. littoralis* promote the mobilization of the *pDv111* element (Evgen'ev *et al*., 1982). The accumulation of hybrid dysfunctions occurs not only by the presence of incompatible alleles, but also by a set of processes related to TE activation. Mechanisms that trigger transposition in hybrids are poorly understood, but it is well known that when two different genomes combine to form a zygote, it must respond to a massive shift in regulatory mechanisms due to this 'genomic shock'.

TE TRANSPOSITION AND EPIGENETIC REGULATION

Genomes have defense systems that avoid TE proliferation, one of the most widely studied systems is the RNA-mediated silencing system controlled by small RNAs (see Blumenstiel (2011) for a review). Two important classes of small RNAs regulate TEs: small interfering RNA and piwi-interacting RNA (piRNA). The first class is associated to Dicer endoribonuclease and has an important role in the control of TEs in plants (Matzke *et al*., 2009). piRNAs mediated the silencing through their interaction with piwi proteins (Vagin *et al*., 2006) and is the main mechanism of animal TE control. In *D. melanogaster*, piRNAs are generated from repeats and TE copies inserted in certain heterochromatic regions named piRNA clusters (Brennecke *et al*., 2007). These piRNAs repress TEs in the germline through a post-transcriptional gene silencing (PTGS), implying the cleavage of transcripts from an active TE, and transcriptional gene silencing by

chromatin modifications (Klenov *et al.*, 2007). Therefore, mechanisms affecting this fine system of TE regulation by PTG mediated by small interference RNAs, together with methylation of promoter regions and chromatin remodeling, could affect TE mobilization. One of the first examples of epigenetic modifications was reported in interspecific kangaroo hybrids, where a high rate of DNA hypomethylation was reported (O'Neill *et al.*, 1998). *D. melanogaster* genome seems to be methylated in coding regions (Salzberg *et al.*, 2004), but the level of methylation is low in *Drosophila* species in general (Marhold *et al.*, 2004). It may be that the main cause of TE derepression in *Drosophila* hybrids is not due to DNA demethylation, but due to the absence of the piRNA specificity provided by the egg. When a TE has already invaded the genome of a species, the piRNA homologous to the TE interacts with its transcripts to induce their degradation. On the other hand, when a TE was introduced in a species that is normally devoid of it, the lack of specific piRNAs, necessary for the repression RNAs, causes the incapacity of inhibiting the TE concerned. For example, when the *D. virilis Penelope* element is introduced into the genome of the distant species *D. melanogaste*r, the piRNAs generated are unable to repress the transposition (Rozhkov *et al.*, 2010a)

In most cases of hybrid dysgenesis, the transposition activation has been attributed to a lack of maternal piRNAs against the target TE, leading to a loss of silencing of this specific TE in the germ cells of progeny (Brennecke *et al.*, 2007, 2008; Chambeyron *et al.*, 2008). This phenomenon has been identified as the main cause of the mobilization of *Penelope* element after intraspecific crosses in *D. virilis* (Rozhkov *et al.*, 2010b). In this case, different TEs are simultaneously mobilized, and the main element (*Penelope*) responsible for the dysgenesis syndrome triggers transposition of other TEs. The mechanism of co-mobilization is not well understood, but it is possible that *Penelope* contains factors that suppress RNA silencing from other TEs (Blumenstiel and Hartl, 2005).

The mobility of *gypsy* and two other retroelements, *Idefix* and *ZAM*, in the somatic follicle cells is controlled by a specific heterochromatic locus located in the X chromosome (Bucheton, 1995). This locus, named *flamenco* in the case of *gypsy*, is responsible for the formation of TE-derived piRNAs that regulate transposon activity through the Piwi pathway (Brennecke *et al.*, 2007). The subtelomeric site 1A, located in the X chromosome (X-TAS locus), contains several *P* element insertions and correspond to another piRNA cluster implied in *P* element silencing in the germline. The site 42AB represents a major source of piRNAs targeting a variety of TEs (Brennecke *et al.*, 2008), including the *I* element involved in hybrid dysgenesis processes associated to I mobilization in germ cells. All these heterochromatic loci generate hundreds of different piRNAs that correspond to transposon targets repeats dispersed throughout the *Drosophila* genome. These piRNAs associate with Piwi proteins and serve as guides that lead to the cleavage of expressed transposon targets. These proteins have an important anti-mobile element activity role demonstrated by the fact that expression of TEs was derepressed in the germline of piwi and aubergine (a Piwi homolog) mutants (Brennecke *et al.*, 2007). Because piRNAs are members of a powerful mechanism of TE control, we can imagine that alterations in this mechanism could be the key to also explain cases of spontaneous transpositions and TE mobilizations linked to stress reported in the literature. Provided that most of piRNAs were derived from heterochromatic insertions of TEs, in a certain orientation at particular sites, their excision from the genome could lead to a deregulation and mobilization of other endogenous TEs. The situation will be restored when a new TE insertion occurs in the cluster region responsible for the production of piRNAs.

WHAT HAPPENS IN NATURE?

Most of the transposition cases in *Drosophila*, described above, refer to laboratory conditions. What is then happening in nature where populations are submitted to different environmental and demographic conditions, and might be confronted simultaneously to different stresses? For example, during colonization processes the new conditions encountered by the founders, in addition to the possibility of crosses with different native species, constitute important sources of stress. Different studies in the invasive species *D. buzzatii* (Labrador *et al.*, 1998; García Guerreiro and Fontdevila, 2001; García Guerreiro and Fontdevila, 2011) and *D. subobscura* (García Guerreiro *et al.*, 2008) showed high occupancy frequency of some TEs in colonizing population compared to original ones. In the same way, increases of *Uhu* and *LOA* elements copy number in Hawaiian *Drosophila* were associated to the colonization of new islands from older islands (Wisotzkey *et al.*, 1997). These transposition increases can be due probably to the different environmental conditions associated to the colonization process. The geographical heterogeneity in TE copy number observed in *D. simulans* natural populations has been attributed to transposition events (Vieira, 1999). This possibility is sustained by the positive correlation observed between the *412* copy number and minimal temperature (Vieira *et al.*, 1998). These authors suggest that the worldwide colonization process of *D. simulans* allowed this species to encounter new environmental conditions susceptible to induce transpositions of TEs. These results could suggest that invasion of new environments may induce epigenetic modifications and then TE activation.

Picot *et al.* (2008) suggested that the variability of *mariner* somatic activity observed *in D. simulans* is more likely due to populational and historical factors than environmental ones, such as temperature. *D. melanogaster* empirical studies in natural populations showed that most TEs were inserted at low frequencies (Charlesworth *et al.*, 1992; Biémont *et al.*, 1994). Theoretical and experimental studies propose that TEs are maintained as a balance between their increase in copy number, by transposition and other opposing forces, including selection, excision and regulation of transposition rates (Charlesworth and Charlesworth, 1983; Charlesworth and Langley, 1989). However, these factors are not the only responsible for the number and distribution of TEs, but other factors such as population size, migration and demographic history may also play significant roles (Lynch and Conery, 2003; Decelière *et al.*, 2005; Lockton *et al.*, 2008). For instance, during colonization processes, the number of founders is reduced, and inbreeding rates could increase in the first stages of colonization. Lynch and Conery (2003) suggest that decreases in Ne as a consequence of population bottlenecks could lead to a fixation of genomic TEs because the effect of negative selection is low. In the same way, Brookfield and Badge (1997) suggested that inbreeding could contribute to a transposition rate increase. However, the implication of inbreeding in transposition rate is debatable because in cases where inbred species present more TE copies than outbred ones, we do not know whether it is due to the inbreeding itself or due to a relaxation in selection pressure, as discussed for *Arabidopsis* (Wright *et al.*, 2001). However, we cannot ignore that inbreeding in *Drosophila* has physiological and phenotypic consequences (Kristensen *et al.*, 2006) that can derive in epigenetic changes. Both inbreeding and epigenetic effects are sensitive to environmental changes, which have an effect on TE regulation and expression (Biémont, 2010).

In the early twentieth century, numerous experiments were performed to estimate the mutation rates in natural populations (Demerec, 1937; Dobzhansky and Spassky, 1963). Most of the methods used involved crosses between wild males and laboratory females;

such crosses are now known to be able to induce transposition. One of the first authors to point out this were Thompson and Woodruff (1980), who observed a release of mutator activity in hybrid individuals resulting from crosses between geographically separated populations. The authors hypothesize that mutator activity could be due to 'insertional sequences' polymorphic in different strains of *D. melanogaster*. With the current state of knowledge about hybrid dysgenesis, the estimations of mutation rates based on this type of crosses could be biased, leading to an overestimation of mutation rates in natural populations.

The general view on natural population is that periods of transposition rate increase, followed by an immediate transposition silencing, which allows TE persistence in populations. This persistence can be increased in elements able to colonize new genomes by horizontal transfer, as reported in large number of TEs in *Drosophila* (see Schaack *et al.* (2010) for a review). Horizontal transfer of an active TE in a naïve genome is a way to allow its propagation by the evasion of TE regulation mechanisms in a new background.

CONCLUDING REMARKS

In *Drosophila*, not all TEs can be mobilized simultaneously by stressful conditions, and elements stable in copy number in a context can be mobilized in another. The huge number of results available in the literature suggests variation in TE stability depending on the host background and the environmental conditions. Environmental and genomic stresses seem to activate transposition in *Drosophila* because of their interference on transposition regulation mechanisms. These mechanisms include different types of small RNAs (small interfering RNAs, piRNAs) and chromatin modification. In cases of genomic stress, crosses between different *Drosophila* lines and/or species affect the piRNA pathway, which results in a derepression of the TEs or of some of them. This is the system of control of many TEs in *Drosophila* as *gypsy* (Pelisson *et al.*, 2007), *P* (Simmons *et al.*, 2007) and *I* (Brennecke *et al.*, 2008), which are usually maternally transmitted. Other elements, as *copia*, have a piRNA suppressor system that seems to involve spermatogenesis-specific mechanisms (Vu and Nuzdhin, 2011). In addition, when a new element was introduced, via interspecific crosses, into the genome of another species, the small interfering RNAs produced are probably incapable of completely inhibiting transcription and transposition of this element in the new host genome.

Stresses can inhibit gene-silencing mechanisms resulting in a reactivation of TEs (Slotkin and Martienssen, 2007), showing that environmental and genomic conditions can influence the epigenetic regulation of TEs. For example, some TEs that respond to stress in *D. melanogaster* contain the same regulatory motifs as heat-shock promoters. Moreover, stress has been considered as a factor important in changing the transcriptional activity of long terminal repeats and adjacent genes in plants (Schramke and Allshire, 2003; Madlung and Coma, 2004). Therefore, the result of stress conditions could be a relaxation of genomic regulation systems, including endogenous TEs.

All the above observations suggest that transposition events, regardless of their origin, can highly increase the evolutionary potential of species. This could lead to the emergence of new phenotypes on which selection could act, contributing to a rapid species evolution. The co-evolution of TEs and host genomes may constitute a way to diminish the detrimental effect of transpositions by the silencing mechanisms. In this way, bursts of TE activity followed by calm periods could occur during evolution even independently of the mechanisms involved. These alternating periods of low and high rate of transposition may be crucial for the generation of genetic variability, and as an effective way to avoid the complete elimination of TEs from host genomes.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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