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Perspective

Intracellular battlegrounds: conflict and cooperation between transposable elements

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Summary

Transposable elements (TEs) are genomic parasites that amplify their own representation on hosts' chromosomes by inserting into new positions. It is traditionally thought that their copy number is regulated by purifying selection that eliminates hosts with higher than average TE abundance. Here, we stress that selection due to beneficial or harmful interactions between TEs introduces a whole new dimension, with implications for TE evolutionary trajectories and TE loads on hosts. This framework poses new questions requiring conceptual and experimental advances. Considering primarily Drosophila data, we make a case for within host selection on TEs by thinking expansively about the lifecycle of several TE families.

Introduction

Transposable elements (TEs) are tiny organisms, with genome sizes varying from hundreds to thousands of nucleotides, that survive by spreading their progeny on host chromosomes (Berg & Howe, 1989). TEs exploit their hosts' ability to transmit chromosomes, and thus inserted TEs, to subsequent generations (Hickey, 1982). In sexual hosts, new habitats become available for TEs to exploit due to recombination between the genomes of sexual partners. In both asexual and sexual hosts, horizontal transmissions might open up new niches for TE spread. The effectiveness of this survival and propagation strategy is illustrated by the presence of TEs in practically all studied organisms. Across species, as much as 10–90% of the genome is represented by TE-derived sequences (Finnegan, 1992).

Just as related organisms are combined into populations and species, related TE sequences are classified into families, the number of which varies from five in *Saccharomyces cerevisiae*, to thirty in *Candida albicans* (Goodwin & Poulter, 2000) to more than fifty in *Drosophila melanogaster* (reviewed by Charlesworth *et al.*, 1994). The number of copies per family per host also varies from several, as for *gyspy* in *D. melanogaster* (Kim *et al.*, 1990) to hundreds of thousands for *LINE1* in humans (Kazazian & Moran, 1998). Different families use different mechanisms to reproduce, and a basic distinction is made between retrovirus-like (long terminal repeat (LTR)-containing) and transposon elements. Retrovirus-like elements transcribe, their transcript is spliced by the host and two to three proteins required for transposition are translated from it. Through the combined efforts of TE and host encoded proteins, the progeny copy is reversely transcribed from an unspliced transcript lacking ends of LTRs, healed into a full-size copy with the template switching mechanism (Arkhipova *et al.*, 1995), and inserted into a host chromosome (Berg & Howe, 1989). *LINE*-type elements (Kazazian *et al.*, 1988) are transcribed from an internal promoter, with the transcript including a complete TE sequence. The transcript is aligned with a nick in a host chromosome, and the nick is repaired with the transcript as a template (Luan *et al.*, 1993). Within the transposon class of elements, the transcript codes a transposase, a protein that cuts the double-stranded TE out of the host's chromosome and inserts it into a new, frequently close by, position. TE copy number increases when the host repairs the double-stranded chromosome break using the transposon-containing homologous chromosome as a template (Engels, 1996). Each class of elements within the community of TEs in a host has the same goal, to reproduce, but they achieve it by different means and have different effects on host performance (Eickbush, 1994).

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The abundance of TEs in host populations will be affected both by selection pressures operating within individual hosts (such as competition between TEs), and by selection pressures operating between hosts with different types and copy numbers of TEs. Most theories of TE evolution consider only selection pressure at the level of the host. When host level selection reduces TE proliferation, models predict that host fitness will still be somewhat reduced relative to what it would be in the absence of TEs. The per-insert decline in fitness has been estimated for multiple types of element as being on the order of 1.4% per insert (Eanes *et al*., 1988; summarized by Nuzhdin & Petrov, 2002). Then, given the estimates of transposition rates measured in populations (Nuzhdin & Mackay, 1995), the fitness of TE-containing hosts should be reduced by 0.5–5% relative to that of TE-free hosts (Charlesworth & Langley, 1989).

Three distinct but not mutually exclusive hypotheses have been proposed as host-level mechanisms of selection against TEs: individual TE copies may be deleterious because they disrupt genes ("gene-disruption model") (Finnegan, 1992); transcription of TEs and translation of TE-encoded proteins may be costly, for instance by transcripts and proteins generating deleterious effects by nicking chromosomes and disrupting cellular processes ("TE-product expression model") (McDonald *et al*., 1997); high copy number of TEs could be deleterious because ectopic recombination among dispersed and heterozygous TEs generates strongly deleterious chromosome rearrangements ("ectopic recombination model") (Montgomery *et al*., 1987).

However, host-level selection is only a part of the story. For TE's, as for other organisms, reproduction (to which new transpositions contribute) can potentially be affected either positively or negatively by the presence of other TEs in their environment. The host cell is a particularly interesting environment in that it has its own genome and is therefore capable of evolving to suppress or facilitate the growth of its transposable elements. However, we will not address TE-host coevolution here since there has been much theoretical and experimental work in this area (see for instance Charlesworth & Langley, 1986; Pelisson *et al*., 1987; Nuzhdin *et al*., 1998; Kidwell & Lisch, 2001). We will solely focus on interactions between TEs that can potentially reduce or increase their probability of transposing, generating selective pressures influencing TE evolutionary trajectories.

Here, we consider how general principles of community ecology and evolutionary ecology may apply (e.g. Pianka, 2000) to interactions between TEs. A similar framework has been used to understand interactions between multiple viruses coexisting within cells, and bacterial pathogens within organisms (Turner & Chao, 1998, Turner *et al*., 1999, Antia *et al*., 1994; Levin *et al*., 1999). Both interactions in which TE's interact physically and those in which they interact by virtue of sharing a resource, have the potential to profoundly affect population sizes and compositions of TE families. Interactions can take the form of parasitism (in which one element benefits at the expense of another), competition (in which both elements are negatively affected by the presence of another), or cooperation (in which both elements benefit from the presence of the other).

While some of our interpretations may be a mile off, we hope to refocus attention on facts that the field has not even known that it forgot to explain (Grebenshikov, 2002). We emphasize that the evolutionary forces discussed might be vanishingly weak (see Charlesworth & Langley, 1986 for explanations); whether they are sufficiently strong to drive TE evolution should be clarified with models.

Parasitism

Parasitism is the exploitation of one organism by another. In many cases parasites are incapable of surviving and multiplying in the absence of a host organism. Just as TEs can be considered genomic parasites, between TEs there are interactions in which the transposition of one element completely depends upon the presence of, and occurs at the expense of, another element. An example of this is the interaction between *SINE*s and *LINE*s (Malik & Eickbush, 1998). *SINE*s are incapable of replicating without *LINE*s and in the presence of *SINE*s, *LINE* replication is dramatically reduced.

LINE transcription is a strange and seemingly inefficient process. *LINE*s are transcribed by *Pol-II* polymerase, but the transcription initiation site is positioned before the promoter region, thus the promoter is included into transcripts from which progeny copies are derived (Figure 1). *SINE*s possess a stronger internal promoter than *LINE*s, as well as a binding site for *LINE* encoded transposase within their 3′ *LINE*-derived end. The *SINE* promoter is recognized by *Pol-III*, an enzyme employed to transcribe vast quantities of small-sized RNA, such as *t-RNA*, which do not require translation. This enables *SINE*s to parasitize *LINE*s by using *LINE* transposase, and to outcompete *LINE*s in the generation of new transpositions (Shedlock & Okada, 2000). The fitness cost per successful *LINE* transposition grows with *SINE* copy number since each *LINE* multiplication is accompanied by multiple *SINE* jumps. This generates strong selection pressure for the host to shut down *LINE* multiplication.

At first glance, the above process does not appear to leave much space for *LINE*s to escape parasitism. As soon as a 5′ truncated copy of a *LINE* element lands just downstream of a strong *Pol-III* promoter, a *SINE*

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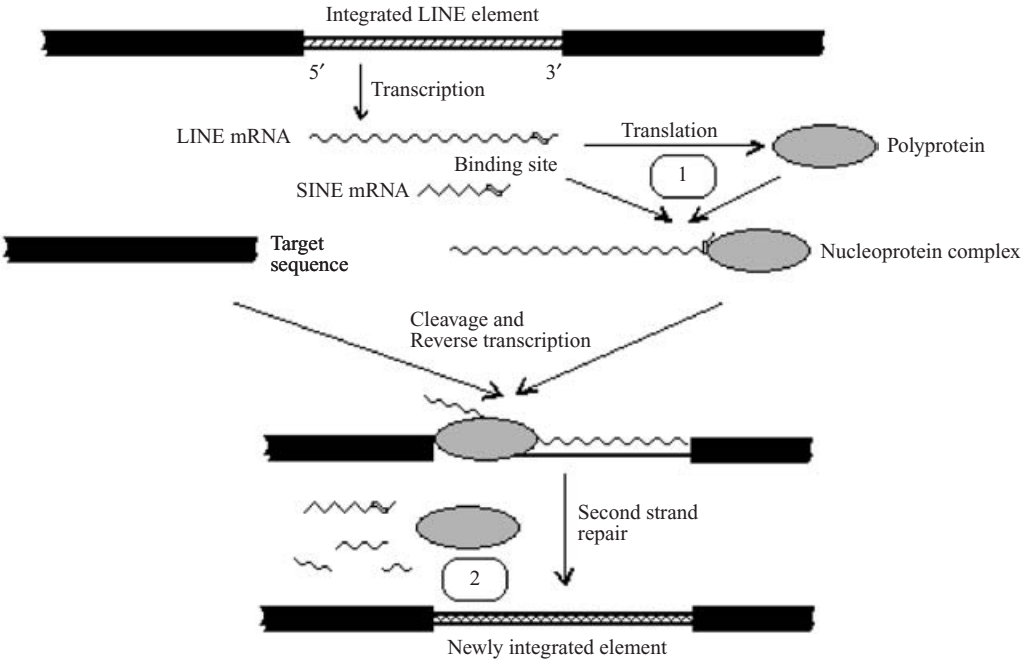

Figure 1. The process of *LINE* transposition, and its exploitation by *SINE*.

is born and the corresponding *LINE* is in trouble. However, while numerous cases of *SINE* explosions and subsequent *LINE* stabilizations are known (Malik & Eickbush, 1998), *LINE*s not exploited by *SINE*s are also known. For example, no *SINE*s have been reported in Drosophila (Pelissier *et al*., 2002). It is not known why, but we speculate that *LINE*s can survive if their transcript manages to stay associated with its transposase after translation (see some experimental support for this in Danilevskaya *et al*., 1994; Martin, 1991; Martin & Branciforte, 1993). Then, *SINE*s can transpose only: (1) if *SINE*s can displace *LINE*s from nucleoprotein complexes or (2) if *SINE*s are capable of re-using transposase which is freed after *LINE* insertions (see Figure 1). The former mechanism should be inefficient since *SINE* transcripts are not co-localized with the *LINE* being translated. The latter process would, perhaps, allow *SINE*s to multiply, but less efficiently than *LINE*s (especially if the proteins involved are short-lived). In fact, it has been shown that a broken copy of the *I* element that does not code for proteins can be complimented *in trans*, but the efficiency with which it transposes is substantially reduced (Pelisson *et al*., 1991). We predict that the extent of cross-mobilization will be much greater for *LINE*s that are exploited by *SINE*s, and encourage experiments to test this hypothesis.

A second case of within-genome parasitism is the interaction between full *P*-element copies and internally deleted ones. Only full copies produce transposase, which generates both direct and indirect costs for these *P*-elements. Direct costs are mediated by decreased host fitness due to the energetic cost of producing transposase, the introduction of nicks in host DNA, and possibly other physiological effects. Indirect costs are those that the *P*-element suffers from insertions of additional *P*-elements in the genome, including from direct costs imposed by their expression and from host-mediated ectopic recombination. Models have demonstrated that these costs may lead to selection for self-regulation of transposition (Brookfield, 1996). *P*-element transposition is, indeed, partially repressed by element-encoded repressors (Gloor *et al*., 1993).

Full elements can suffer the costs of transposition outlined above without receiving the benefits of increased multiplication. Transposase produced by a full copy is equally available to all elements in the genome; transposase is translated in the cytoplasm, travels back to the nucleus where it finds any *P*-element inserted into host DNA, cuts it out, and inserts it into a new, frequently close-by, position. Ironically, a full copy suffers lesser costs when a deleted element jumps, since deleted elements will not reduce host fitness by producing additional transposase. Copies that jump without producing transposase act as parasites on those that do, by receiving a within host benefit without paying a cost.

If full copies of *P*-elements are selected against at the level of the host because of the costs of transposition, why are they present? We suggest this results from spatial structure: transpositions happening within a host are affected solely by its P element community rather than that of the whole host population. New transpositions occur only in hosts with at least one full copy, so the average number of copies of both full and truncated elements in these hosts increases. Truncated copies also occur in hosts in which no transpositions occur. Hosts with full copies have lower fitness, thus

the frequency of these hosts declines. When mating occurs, TEs spread into new lineages. If there is sufficient transposition of full copies within infected hosts, this replication can balance the loss of full copies due to host level selection and lead to a stable equilibrium number of full copies in the population. The mean and variance in the proportion of active copies within individual flies, transposition rates of full and broken elements, and the cost each type of transposition generates from the perspectives of the host, the full copy, and the broken copy, need to be quantified to evaluate our hypothesis.

Several alternative explanations have been proposed. Brookfield (1996) has shown that broken elements, which act as repressors, might stabilize the proportion of active copies. Hartl *et al*. (see 1997 for review) proposed a ''horizontal transfer'' model for survival of *mariner* transposon, based on the recognition that only active copies can be horizontally transferred between species, and subsequently replicate. Horizontally transmitted elements spread within their new species, and transfer rates must be high enough that they are likely to escape to a new host before defective copies take over. While exciting, this hypothesis relies on transposons to adopt a risky strategy with frequent dispersal to unknown new hosts, rather than having an evolutionary stable strategy of maintenance within a species.

Competition

Competitive interactions can be broadly classified into those in which organisms compete by virtue of sharing a resource (consumptive/exploitative, or pre-emptive when space is the limiting resource and the organism arriving first wins), and those in which there are additionally antagonistic interactions between the organisms (interference competition) (Pianka, 2000). When competition occurs, the net level of resource depletion is less than the sum of resource depletion by the two species when each is alone.

Resource competition among TEs could occur for: metabolic components needed for transposition; space in the genome or available target sequences; the number of transposition-generated repairs the host can sustain in one generation; and the general costs of depleted host vigor. Overall, host fitness decreases as the total number of TEs increases (Pasyukova *et al*., 2002; Nuzhdin & Petrov, 2002). With rare exceptions, each TE will have higher fitness in the absence of other elements because host reproduction will be higher (see Charlesworth & Langley, 1989 for explanation of why deleterious effects of TE copies should be epistatic for TE copy number not to grow). In conditions in which there is competition for resources, soft selection (in which fitness depends on the characteristics of competitors) occurs. Contrary to the traditional kin-selection based view, recent models have shown that when parasites are less-closely related, soft selection can result in lower virulence to the host because it selects for parasites that repress each other rather than increase their own reproduction (Chao *et al*., 2000). Thus, antagonism toward another TE would benefit the antagonistic TE by partially regulating total TE abundance without the personal cost of decreased transposition. We hypothesise that antagonistic interactions between elements (''cross repression'') are an important hitherto unexplored force acting to prevent TE explosions, and to reduce the deleterious cost of TEs to hosts.

There is an under-acknowledged contradiction between the ''accepted'' TE theory, which is the theoretical prediction that elements should evolve to the highest rate of transposition possible (Charlesworth & Langley, 1986; see for review Charlesworth *et al*., 1994), and the multiple empirical observations that some TEs clearly suppress themselves. One of the best-known cases of self-suppression is that of the *micropia* retrovirus-like element. In addition to the 5′ LTR initiated transcript, this element also transcribes from the 3′ LTR. This generates double-stranded RNA and suppresses transposition (Lankenau *et al*., 1994), perhaps through an RNAi like mechanism (see for review Plasterk, 2002). Rather than transposing at the highest rate possible, this element appears to reduce the number of *micropia* transpositions – why would it do so? We hypothesize that the *micropia* copy might be reducing not its own transposition activity, but that of other *micropia* copies in the genome; 3′ transcription may be an aggressive attempt to sabotage one's competitors. Indeed, there are likely to be negative temporal correlations between transcription from the two promoters (5′-direct and 3′-inverted) within a copy, but not between copies. If co-timed expression leads to formation of double-stranded RNAs that are then inactivated, the 3′ transcribing *micropia* will inactivate transpositions of other *micropia* copies without harming its own multiplication, which is dependent on the 5′ LTR initiated transcript only.

Another interesting case of detrimental cross-talk between different TE copies within a family is for the *mariner* transposon. *mariner* transposase is a multimer, enabling elements to directly affect each other's transposition rate. When flies are infected by a *mariner* element with a mutant transposase, the rate of transposition of wild-type *mariner*s decreases (Lone *et al*., 1996). Furthermore, over-production of wild-type transposase decreases the per copy rate of transposition instead of increasing it. We suggest that when *mariner* transposition activity is excessive to the point where it could harm the host, copies benefit more from suppressing transposition of others than from increasing their own transposition (see similar ideas for phages in Chao *et al*., 2000). Both the *micropia* and

mariner stories call for experiments testing whether, indeed, an element faced with the declining fitness of its hosts depresses the transposition of its compatriots more than itself.

A case of competitive interactions between different TE families is illustrated by *hobo* and *Hermes* transposons. Vectors containing transposase binding sites were engineered from *hobo* cloned from *D. melanogaster* (Streck *et al*., 1986) and used to transform other species by co-injecting with a helper plasmid bearing functional *hobo* transposase. In *Musca domestica*, *hobo*-based inserts were unstable in the absence of the helper plasmid (Atkinson *et al*., 1993). Sundararajan *et al*. (1999) explained this by the ability of the transposase encoded by *M. domestica Hermes* element to cross-mobilize *hobo*. The *Hermes* transposase was much less efficient in mobilizing *hobo* in comparison with *Hermes* itself. The efficiency of *hobo* encoded transposase was comparable for both substrates. At first it appears that *Hermes* might multiply at the expense of *hobo*, displacing it from the host. However, closer observation shows that all of the *hobo*-mediated *Hermes* excisions were imprecise, suggesting that *Hermes* functionality was damaged in both the previously occupied site and potentially in the new insertion site. Thus, *hobo*-encoded transposase was directly harming *Hermes*. Whether the above example is a peculiar artifact of transposition machinery, or an adaptation evolved in elements frequently undergoing horizontal transfers (Kidwell & Lisch, 2001) is open to both debate and experiments.

Cooperation

The difficulty in maintaining cooperation is suppression of cheaters, individuals who attempt to gain from the cooperative efforts of others, but do not themselves cooperate. Evolutionary biologists have developed four distinct types of models to explain the existence of cooperation: reciprocal altruism, by-product mutualism, kin selection, and group selection (Dugatkin, 1997). Of these, reciprocal altruism does not appear relevant for TEs since it requires recognizing and retaliating against cheaters, something TEs are unlikely to be smart enough to do. In by-product mutualism, it is immediately more beneficial to cooperate than it is to cheat. Kin selection is based on the concept of inclusive fitness – it is worth engaging in personally costly actions if the benefit to the actor's relatives (b), scaled by their relatedness to the actor (r), outweighs the costs to the actor (c) (Hamilton's Rule: $rb\text{-}c > 0$). Group selection models require that cooperative groups are more successful than groups with higher proportions of cheaters – thus, within groups the frequency of cheaters will increase, but selection acting between groups will remove groups with too high a proportion of cheaters. Here, we outline a few examples of cooperation between TEs, and provide an explanation for one of them.

Transposition of retrovirus-like elements requires multiple proteins including gag, RT, and RNAaseH. These are coded by 2-3 ORFs contained in a single transcript. While some families of TEs produce multiple proteins via a frame shifting mechanism and/or protein cleavage, others splice the transcript (Arkhipova *et al*., 1995). The latter mechanism involves cooperation, and makes TE families practicing it particularly susceptible to the evolution of cheaters. Suppose a mutation occurred in a copy from the *gypsy* family of LTR-containing elements (Berg & Howe, 1989) which destroyed the splicing signal. We indeed know that Drosophila stocks vary in the abundance of spliced *gypsy* transcript and this variation is associated with the presence of particular *gypsy* sequence variants and/or alleles of the host *flamenco* gene (for more detail, see Kim *et al*., 1994; Lyubomirskaya *et al*., 1990; 1993; Pelisson *et al*., 1994; 1997). This mutant copy would not produce proteins required for transposition, but could still transpose when proteins were provided by an "altruistic" element. Further, the "altruistic" element would have inferior transposition compared to the mutant "cheater", since a fraction of the "altruist"-encoded transcripts splice and can no longer be used as transposition templates. Similarly, formation of virus-like particles is a process requiring cooperation between *copia* family elements. VLPs are comprised of two full-size transcripts (plus proteins translated from these or other transcripts) and a protein translated from a third spliced transcript. A VLP gives birth to a single progeny copy, read from just one out of at least three participating transcripts (Yoshioka *et al*., 1990). We do not know why these cases of cooperation are evolutionary stable.

Perhaps, the best case of cooperation is the *Het-A* element, a non-LTR retrotransposon that inserts into telomeres. Elements are sequentially added onto chromosome ends with their 3′ end closer to the chromosome interior. Non-LTR elements typically have their promoters downstream of their transposition initiation site, within the 5′ non-translated region. Intriguingly, however, assays of reporter gene expression in Drosophila cell culture lines have demonstrated that the 5′ untranslated region has little to no promoter activity on its own while 3′ sequences show strong promoter ability (Danilevskaya *et al*., 1997). The 3′ promoter turns out to be comprised of several sequences, with activity greatest when all are included, and activity further augmented by the presence of the 5′ sequences (Danilevskaya *et al*., 1997). Thus, rather than each element containing its own promoter, it instead uses the promoter of its upstream neighbor as an external promoter. As each new element inserts on the end of the chromosome, it directs transcription of its downstream neighbor but is not

itself transcribed until another element inserts upstream of it. Newly inserted copies are always derived from some *HetA* copy other than the one they will transcribe. It is most natural to think of the cooperation in this system as due to group selection. If a copy "cheated" and did not transcribe its neighbor it would benefit in the short term, since a new element would still jump next to it and the cheater would subsequently be transcribed. When rare, cheater transcript would then be overrepresented relative to actual cheater copy number in the telomere, since cheaters would not transcribe their non-cheating neighbors. However, once the cheater forms too high a proportion of total copies it's in trouble; if a cheater is abundant in a telomere it will often be next to other cheaters thus not transcribed, and if a cheater is the first copy to insert on a chromosome then the host organism will be dead since the telomeres will not extend further. Thus groups (i.e. flies) that have too high a proportion of cheater *HetA*s will have less offspring, reducing the net fitness of their *HetA* copies.

Conclusions

The study of TEs has long been dominated by the two goals of understanding the fitness consequences of TEs on their hosts and understanding the population dynamics of particular TEs within host lineages. We suggest that the time has come for TE biologists to move from studying single species population dynamics to viewing cells as ecosystems, and TEs as organisms in a community, capable of both harming and helping each other. The examples we present above are likely only to scrape the surface of the variety of mechanisms by which TEs may interact with each other and affect one another's fitness. Above we present a number of hypotheses, at times very speculative, to explain both the evolution and consequences of various interactions between TEs – we urge both experimentalists and theoreticians to test these ideas. Even if right only 10% of the time, these interactions will not only affect the evolutionary trajectories of individual TE families – whose environment importantly contains not just the host but each other – but have the potential to affect the net virulence of TEs on hosts, and may even act as a novel mechanism of TE control.

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