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REVIEW

The contribution of transposable elements to transcriptional novelty in plants: the *FLC* affair

Leandro Quadrana

Institut de Biologie de l'Ecole Normale Supérieure (IBENS), Centre National de la Recherche Scientifique (CNRS), Institut National de la Santé et de la Recherche Médicale (INSERM), Ecole Normale Supérieure, PSL Research University, Paris, France

ABSTRACT

Transposable elements (TEs) are repetitive DNA sequences with the ability to replicate across genomes and generate mutations with major transcriptional effects. Epigenetic silencing mechanisms that target TEs to limit their activity, including DNA methylation, add to the range of gene expression variants generated by TEs. Here, using the iconic gene flowering locus C (*FLC*) as a case study I discuss the multiple ways by which TEs can affect the expression of genes and contribute to the adaptation of plants to changing environments

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Introduction

Transposable elements (TEs) are parasitic DNA sequences that have the ability to self-propagate and account for an important fraction of plant genomes [1]. Most genomes appear to contain a mixture of TE types in various states of evolutionary decay. TEs can be classified in two broad types: Class I retrotransposons, which are mobilized using a "copy and paste" mechanism and Class II DNA transposons, which transpose through a "cut and paste" mechanism. Remarkably, the contribution of these two types of TEs differs largely between species, with the LTR-containing retrotransposons being the most abundant in plant genomes [2].

First considered as an oddity following their discovery by Barbara McClintock [3], then as junk DNA [4], now TEs are universally acknowledged as major drivers of genome evolution [5]. For instance, genome size variation between species mainly results from differences in TE content [2]. Moreover, domestication of TE sequences has contributed to the evolution of new proteins and cellular functions [6,7]. A paradigmatic example of this process is the repurposing of a TE transposase to give rise to a pair of transcription factors, FHY3 and FAR1, that modulate light signaling in plants [8].

Similarly, the domestication of another transposase, related to the Harbinger family of DNA transposons, is at the origin of ALP1, a conserved component of the Polycomb Repressive complex 2 (PRC2) in plants [9]. Moreover, because TEs can be sensitive to the environment and contain transcription factors binding sites [10–12], their mobilization can also contribute to the rewiring of gene regulatory networks, as was proposed by a recent burst of the cold-responsive mPing transposons in rice [13]. In contrast to the well-documented importance of TEs to the macroevolutionary process [14], our knowledge of the contribution of ongoing transposition to within-species variation is only starting to be fully appreciated thanks to the wealth of genomic data now available.

TEs pose multiple threats to the physical and functional integrity of genomes by providing abundant substrates for unequal crossing over that can lead to chromosomal deletions, duplications, inversions, and translocations. TEs can also disrupt genes through insertion, generate excision "footprints" in the case of DNA transposons, and shuffle small stretches of flanking DNA around the genome through transduction-like processes [1]. Nonetheless, we now know that TE mobilization might sometimes create beneficial alleles, as was demonstrated by the TE-induced

CONTACT Leandro Quadrana leandro.quadrana@ens.psl.eu Institut de Biologie de l'Ecole Normale Supérieure (IBENS), Centre National de la Recherche Scientifique (CNRS), Institut National de la Santé et de la Recherche Médicale (INSERM), Ecole Normale Supérieure, PSL Research University, Paris 75005, France

mutations in the gene *tb1* underlying maize domestication [15]. Similarly, a rare TE insertion within the gene *PSY1* in tomato is responsible for the pale yellow coloration of same tomato fruits [16]. Furthermore, epigenetic silencing mechanisms that target TEs to limit their activity, including DNA methylation in plants and mammals, add to the range of gene expression variants generated by TEs [17]. In plants, cytosine can be methylated in the three possible contexts, i.e. CG, CHG and CHH. In A. thaliana, the RNA-directed DNA methylation (RdDM) pathway, which is instructed by small interfering (si)RNAs, plays a central role in *de novo* DNA methylation of TEs and other repeat sequences [18]. Once stablished, DNA methylation at CG sites is maintained by the DNA methyltransferase MET1, which recognize hemymethylated CGs generated upon DNA replication. In contrast, CHG sites are methylated by the plant-specific chromomethylases CMT2 and CMT3 on a self-reinforcing loop with H3K9me2 [19]. Methylation of CHH sites, which are nonsymmetrical, is maintained by RdDM over short TEs and by CMT2 for internal parts of long TEs [20]. Despite the multiple mechanisms in place, DNA methylation changes over TEs can occur few generations after their integrate into new places [21,22], spontaneously [23,24], during *in vitro* culture [25] or in response to environmental cues [10,26,27]. At least in plants, changes in the DNA methylation state of TE sequences are particularly prone to be inherited, with potential transgenerational phenotypic consequences [17]. Thus, the type of gene expression changes caused by TE insertions is likely much more diverse than that generated by SNPs.

FLC as a platform to study the transcriptional impact of TE insertions

Population genomic studies performed across numerous, distantly related, plant species agree that new TE insertions tend to accumulate evenly across chromosomes [28–30]. Despite the even distribution at the chromosomal level, certain *loci* accumulate higher number of TE-insertions than expected by chance. For instance, analyis of resequencing data for 210 wild *A. thaliana* accessions identified few genes with a high load of TE insertions, including genes involved in immune response [30]. Studies in other plant species, including tomato [16], uncover similar TE insertion patterns. Such enrichments result from preferential integration of TEs together with selective biases [31]. Indeed, *COPIA* LTR-retrotransposons, a class of TEs remarkably active in plant genomes, integrates preferentially in nucleosomes containing the histone variant H2A.Z [22] which is enriched in the body of environmentally responsive genes [32]. The highest number of independent TE insertions within a gene concerns *FLC*, which encodes a key transcription regulator that repress expression of flowering factors such as SUPRESSOR OF CO1 (SOC1), FLOWERING LOCUS T (FT) and FLOWERING LOCUS D (FD) required for vernalization response in *A. thaliana*. Interestingly, the gene body of *FLC* has low levels of H2A.Z, suggesting that the accumulation of TE insertions in this locus is more likely due to selective constraints rather than to preferential integration. Reducing or losing the requirement for vernalization can facilitate adaptation to habitats with high summer drought or other high mortality situations that require fast life cycling, whereas increasing vernalization may be selected in northern latitudes. Consistent with the importance of vernalization for local adaptation, multiple *FLC* alleles affecting flowering time have been identified in *A. thaliana* [33], including numerous TE-containing alleles [30]. The large number of TE-containing alleles of *FLC* is not specific to *A. thaliana*, as such types of alleles are also found in other Brassicaceae species (Figure 1). Thus, recurrent TE-induced mutations at *FLC* may represent a common strategy to rapidly cope with new environments. Incidentally, the large number of TE-containing alleles of *FLC* provides a unique system to investigate the contribution of TEs to the generation of gene expression and phenotypic changes.

An unusually long intron integrates the epigenetic regulation of *FLC*

Vernalization is the acceleration of flowering by prolonged cold, which transcriptionally repress *FLC* and induces epigenetic silencing mainly via the methylation of histones H3K27 by PRC2 [34]. Although *FLC*-like genes were initially thought to be restricted to the Brassicaceae, comparative genomic analyses identify *FLC-like* genes in diverse eudicots, including monocots, where they can also act as vernalization-regulated floral

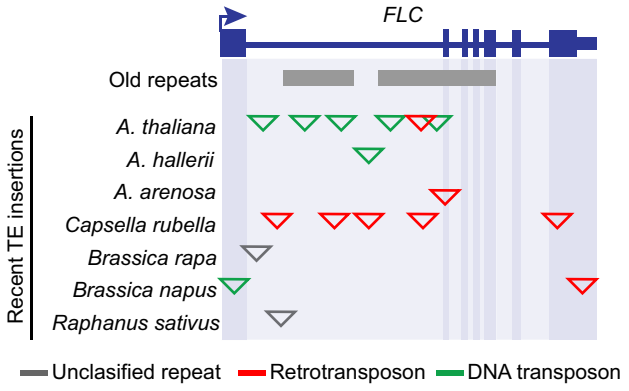

Figure 1. TE insertions and other repeats detected in *FLC*. Boxes and triangles indicate the position and type of repeats (unclassified, retrotransposon and DNA transposons) identified in natural accessions of different Brassicaceae species.

repressors [35]. Nonetheless, all Brassicaceae *FLC* genes share an atypical genic structure characterized by an exceptionally long and conserved first intron, which is the primary target of PRC2-mediated epigenetic. Despite its importance for the epigenetic regulation of *FLC*, the evolutionary origin of this intron is not well understood. In *A. thaliana*, most long introns seem to derived from TEs and are enriched in heterochromatic TE sequences [36]. One exception to this trend is the first intron of *FLC*, which has neither well annotated TE sequences nor epigenetic modification associated with TE silencing. However, a recent deep repeat annotation revealed traces of uncharacterized TEs within *FLC* [37]. Interestingly, numerous TEs that lose DNA methylation in mutants deficient in *MET1* or the chromatin remodeler DDM1, as well as in the endosperm of wild-type seeds, gain ectopic H3K27me3 [38–41], indicating that unmethylated TEs can be targeted by PCR2. Therefore, it is reasonable to speculate that the accumulation of old, highly degenerated and unmethylated TE sequences within *FLC* may have contributed to the evolution of this notable intron and its epigenetic regulation.

Population genomics studies in *A. thaliana* revealed that most natural TE insertions detected near *FLC* locate within the first intron [30]. Similarly, insertions of uncharacterized transposable elements have been detected in the first intron of *FLC* in *Brasicca rapa* [42] and radish [43], indicating that TEs have targeted recurrently this intron. Notwithstanding the frequent structural variants observed, the size of *FLC*'s first intron is relatively conserved across Brassicaceae species, suggesting that its length is itself under Darwinian selection, likely because it is functionally relevant. Mathematical modeling estimates that the a large number of nucleosomes, and therefore length, at *FLC* is a critical factor for the maintenance of its chromatin-based epigenetic memory [44,45], which would otherwise require continuous reinstruction by *trans* modifiers [46,47]. Therefore, transposition may have served as a powerful source of sequences that contributed to the long-term evolution of *FLC* epigenetic regulation.

TE-induced loss-of-function mutations

A comprehensive population genomic study of TE insertions using sequencing data for ~300 *A. arenosa* individuals identified an excess of recent insertions in autopolyploids compared to diploids. This excess was attributed to relaxed purifying selection in polyploids, known as polysomic masking, rather than transposition bursts after polyploidization [28]. Thus, TE over-accumulation in polyploids provides an excess of major effect mutations that may facilitate local adaptation, consistent with the higher colonization potential frequently documented in polyploids compared to their diploid progenitors. A textbook example of such adaptive potential is the successful colonization of railway ballasts by *A. arenosa* tetraploids. Railway populations flower earlier and this was associated with loss of *FLC* expression [48]. However, because *A. arenosa* contains two *FLC* paralogues (*AaFLC1* & *AaFLC2*) arranged in a complex locus, the causal mutation underlying the early flowering was unknown [48]. Target sequencing of *FLC* paralogous across *A. arenosa* populations revealed a fragmented *COPIA* LTR retroelement insertion in the second exon of *AaFLC1*, which is the main contributor (>80%) to total *FLC* expression in *A. arenosa*. The exonic *COPIA* insertion was exclusively found in tetraploids populations collected in railways and is associated with the strong reduction in *FLC* expression and early flowering, providing a compelling example of the potential brought by TEs to enable rapid adaptation to novel habitats.

Another TE derived loss-of-function allele was identified in a genome wide association study (GWAS) for flowering time variation in *Brassica napus*. A single identified an exonic TE insertion in one of the three paralogous of *FLC* (*BnaA02.FLC*) [49]. The exonic insertion corresponds to a fragmented hAT DNA transposon and was also linked to reduced *FLC* expression and flowering time. Although a detailed molecular characterization of the transcriptional impact of these insertions is lacking, they likely truncate the transcript trough premature transcription termination and/or encode nonfunctional protein products as was demonstrated for other exonic insertions [50].

Natural loss-of-functional *FLC* alleles generated by exonic TE insertions have been so far detected only in polyploids, which is consistent with polyploids populations being able to tolerate such recessive alleles. Conversely, diploids are expected to purge more rapidly highly deleterious mutations, as was demonstrated by comparing diploid and tetraploid populations of *A. arenosa* [51]. Indeed, multiple *FLC* alleles with TE insertions within non-coding regions of genes, which likely cause hypomorphic or gain of function mutations, have been identified in diploids (see below).

TE-mediated mRNA destabilization of *FLC*

mRNA expression levels result from a balance between transcription and degradation. The regulation of these two processes determine the turnover rate of each mRNA and enables organisms to rapidly respond to environmental changes.

Examination of natural alleles of *FLC* in 35 *Capsella rubella* accessions revealed multiple TE insertions [52]. These TEs are located in non-coding regions of *FLC*, i.e. first intron and the 3 untranslated region (UTR) and associated with early flowering. Fine mapping and complementation experiments demonstrated that at least one of these TE insertions, which corresponds to an helitron TE located in the 3 UTR region of *FLC*, was responsible for the early flowering. This helitron insertion incorporates a pair of AU-rich elements (AREs) within the 3 UTR region, which are known to induce 3 -to -5 mRNA degradation mediated by the exosome complex [53]. Using Luciferase reporter assays the authors demonstrated that these additional AREs can reduce the stability of *FLC* mRNAs, therefore decreasing its expression level and permitting the transition from vegetative to reproductive growth.

Epigenetic regulation of *FLC* by intronic TEs

In a forward genetic screen to identify factors involved in the specification of reproductive organ identities, a mutant in the gene *HEN1*, which is required for the production of siRNAs, was found to delay flowering time [54]. Remarkably, only *hen1* mutants in the Ler background display this phenotype because of the presence of a Ler-specific intronic TE insertion within *FLC*. This intronic insertion puts *FLC* under the control of siRNAs, which dampen its expression likely through post-transcriptional gene silencing (PTGS) and accelerate flowering. Strikingly, a recent forward genetic screen to identify factors regulating the expression of this TE found that RdDM-dependent DNA methylation suppress the expression of a cryptic transcript initiated at the intronic TE via transcriptional gene silencing (TGS) [55]. A shift in the use of the canonical or cryptic TSS reduce the levels of full-length *FLC* transcripts as well as flowering time. This two set of results highlight the multiplicity of epigenetic regulations that can be contributed by an intronic TE.

An independent natural allele of *FLC* associated with variation in DNA methylation over an intronic SINE-like non-LTR retroelement has been identified in *A. hallerii* [56], which propagates clonally and has a perennial life-cycle [57]. Similarly to its role in other perennial Brassicaceae, such as *A. alpina* [58], *FLC* expression in *A. hallerii* is regulated seasonally and suppresses flowering when upregulated. To assess the role of DNA methylation in seasonal responses, the authors collected samples from the same clonal plant acoss the year and produced whole-genome bisulfite sequencing (WGBS) [56]. Remarkably, the SINE-like insertion in the first intron of *FLC* showed a seasonal change in CHH methylation, with methylation levels in March and June being the highest and lowest, respectively. Consistent with a common role of DNA methylation in transcriptional silencing, high CHH methylation at the SINE-like insertion associates with low *FLC*

expression, supporting the notion that epigenetic silencing of intragenic TEs can contribute to the transcriptional regulation of genes in response to environmental cues. Nonetheless, whether variation in CHH methylation levels are the cause or the consequence of the seasonal change in *FLC* expression remains to be determined.

TEs expand the environmental response of *FLC*

Plant TEs are remarkably sensitive to the environment, as was first proposed by Barbara McClintock [59]. Transcriptional activation of TEs has been observed in response to a wide range of stresses, including salt [60], cold [13], callus formation [61], heat [62] and biotic stresses [63,64]. Indeed, some TEs contain binding sites for stress-responsive transcription factors. For instance, the *A. thaliana* LTR-retrotransposon *ATCOPIA78* harbors several binding sites for heat-shock factors (HSF), which are able to drive transient transcriptional activation of *ATCOPIA78* following heat shock [10]. These binding sites are present among *ATCOPIA78-like* retrotransposons from other Brassicaceae species, however their acquisition and conservation seems to be species specific, consistent with recurrent evolution of heat-responsiveness [12]. To study whether this capacity of *ATCOPIA78* to respond to heat-stress can provide new transcriptional regulations to *FLC*, we investigated a natural *ATCOPIA78* insertion located within the first intron of *FLC* in the Ag-0 accession [30]. This TE-containing allele of *FLC* is very rare, suggesting that it was generated recently. Notably, plants carrying this intronic insertion are late flowering and require long vernalization, indicating that *FLC* is fully functional. However, when plants are subjected to heat shock at the seedling stage, *FLC* expression is markedly reduced and plants flower early, likely as a result of the transient epigenetic reactivation of *ATCOPIA78* (Figure 2). How silencing of *FLC* was subsequently maintained to allow flowering remains to be determined, but it is tempting to speculate that the PRC2-based memory system involved in the long-term silencing of *FLC* in the context of vernalization [65] is also at play here. Alternatively, heat-induced *ATCOPIA78* transcripts may generate siRNAs, which direct TGS to the cognate TE copy together with the *FLC* locus. Given that Ag-0 was collected from a site (Southwest of France) with non-vernalizing winters, the acquisition of *ATCOPIA78* within this haplotype might have enabled the local adaptation of Ag-0 by endowing it with the ability to flower early even in the absence of vernalization but in response to hot summers [22].

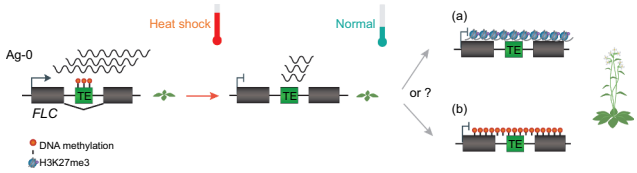

Figure 2. An intronic insertion expands the environmental response of *FLC*. The natural accession Ag-0 contains an intronic insertion of a heat-responsive TE within *FLC*. Following heat-stress at the seedling stage the TE-containing allele of *FLC* becomes stably silenced and induces early flowering in the absence of vernalization. Long-term silencing of *FLC* following heat shock could be due to (a) facilitating PRC2-based deposition of the repressive mark H3K27me3 or (b) de novo DNA methylation of *FLC*.

Concluding remarks

Given the large number of TE-induced mutations as well as the great knowledge we have about its regulation, *FLC* provides a unique opportunity to study the role of transposition in the creation of relevant transcriptional and phenotypic variation. Population genomics approaches are relatively recent and I anticipate that many additional rare alleles of *FLC* caused by TE insertions will be uncovered in the future. Because TE mobilization generates large effect mutations upon insertion, the type of TE-derived alleles that can be observed in nature are strongly constrained by natural selection. Indeed, with the notable exception of *FLC*, population genomic studies have not detected TE insertions at other *loci* encoding factors involved in flowering time, such as *FT*, *SD* or *SOC1*. Thus, natural TE insertions provide powerful systems to examine how new mutations, especially those with large effects, contribute to novel transcriptional regulations influencing adaptive evolution.

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Disclosure statement

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