Submitted: 11/11/2020

Review Article

[1]Department of Biology, McGill University, Montreal, QC, Canada

Keywords

Transposable elements, genomics, evolution, stress, molecular biology, epigenetic

Email Correspondence

oscar.dumoulin@mail.mcgill.ca

Oscar Dumoulin[1]

The Role of Stress in the Spread of Transposable Elements

Abstract

Background: Transposable elements (TEs) and genomes have been at war for millions of years. On one hand, genomes developed epigenetic systems to inactivate TEs. On the other hand, it appears that TEs can take advantage of stress to evade the genome's repressing systems and spread throughout the genome. However, until recently it was unclear how and why stress influences transposable elements' movement. In this review, we explore the mechanisms involved in TE stress-induced activation.

Methods: The first part of the review looks into epigenetic mechanisms, its 19 references were taken from Handbook of Epigenetics 2nd edition (1) and reviews (2) (3). The rest of the studies presented in this review were drawn from searches done on Web of Science with the terms: TS=((Transposable element* OR mobile genetic element*) AND (Stress or Evolution) AND (Activation)) with peer-reviewed articles and reviews written in English included only. The search yielded 401 results and 56 were estimated relevant and of sufficient quality to be selected.

Summary: The main conclusion reached by this review is that protection mechanisms against TEs movement, which are mostly epigenetic, are compromised by the presence of stress. Additionally, TEs themselves evolved diverse tools to promote their activation under certain stress conditions allowing them to evade the repression imposed by the genome. These two mechanisms provide opportunities for TEs to move around the genome and create genetic diversity during stress episodes. As such, TEs stress induced mobility certainly played a major role in the rapid adaption of populations and its impact can be witnessed across genomes.

Introduction

McClintock's discovery of transposable elements (TEs) in maize (4) unveiled the genome as a dynamic playground for mobile DNA sequences. TEs are ubiquitous, mostly repetitive, short DNA sequences that move from one location to another location in the genome, often creating a duplicate copy in the process. As sequencing techniques and our capacity to recognize transposable elements progressed, the genome appeared to be more of a battlefield, where TEs colonized a considerable part of eukaryote's genomes. In fact, biologists were startled to observe that TEs related sequences could constitute up to 85% of an organisms' genome. (5) It became necessary to understand the nature of TEs and explain their overwhelming presence in genomes. Dawkins and others (6, 7) hypothesized that TEs were selfish, self-replicating elements, serving no purpose to the genome. However, McClintock suggested that TEs were, instead, an important source of genetic variation, involved in regulatory networks and likely activated by stress. (8)

The observation of active TE families with transposition rates three orders superior to mutation rates have definitively established TEs as a source of variation and material for selection. (9, 10) Moreover, the discovery of TE families and individual insertions domesticated by genomes (11, 12), coupled to the discovery of TEs responding to stress and TEs involved in regulatory networks (13, 14) ruled out the view of TEs as junk DNA and proved McClintock right.

In addition to being a source of variation, TEs are themselves highly variable elements. The classification proposed by Wicker et al. (15) is the predominant system used in the literature to describe TEs. The classification divides TEs into two major classes, Class I (retrotransposons) replicating through an RNA intermediate and Class II (DNA transposons), which do not utilize an RNA intermediate to spread. Further sub-classification characterizes TEs as part of families and orders. (15)

For a long time, only the phenotypic consequences of TE activation -which describes the movement and spread of TEs- could be studied. Yet, it was enough to observe that organisms exposed to stress displayed increased TE activity. (8, 16, 17) The mechanisms underlying the activation of TEs remained elusive for a long time following TE's discovery until, as we will see, recent findings in the field of epigenetics have allowed us to discern the processes governing TE stress-induced activation.

In this review, we will first look at the known mechanisms involved in TE repression. Using our current understanding of repression mechanisms, we will, in a second part, study how stress affects silencing pathways and elicits TE activation. Finally, we will discuss how TE activation impacts organisms at the genetic, phenotypic and evolutionary level.

Genome's weapons against transposable elements activity

Under the threat of spreading transposable elements, the eukaryotic genome has developed a set of tools operating at multiple levels to turn mobile elements immobile. In fact, it has been hypothesized that epigenetic mechanisms involved in gene regulation such as DNA methylation and RNA interference (RNAi), first evolved as defense systems against TEs. (18) In this part, we will draw our attention towards the three main mechanisms developed by eukaryotes to repress TEs, namely RNAi, DNA methylation and histone modification. In addition, we will take a look at the Repeat-Induced Point (RIP) mutation system present in Neurospora.

RNAi

The main tool used by eukaryotic cells and genomes to counter TE activity is the RNAi system. RNAi uses RNA precursors to silence post-transcriptionally foreign DNA and TEs. Indeed, it is hypothesized that RNAi evolved as a defense against viruses and TEs. (19) Among vertebrates, the RNAi system is differentiated between the germinal and somatic cells.

In germinal cell lines, the piwi-interacting RNA (piRNA) pathway is involved, while in somatic cells it is the small-interfering and micro-interfering RNA (si- & miRNA). The repressing mechanisms employed by PIWI/piRNA and, siRNA & miRNA are similar, and only differ in the proteins involved, type of RNA used and their targets. (20) The PIWI/piRNA pathway represses TEs in germinal cells and prevents the uncontrolled spread of TEs in the next generation. (21-23) Indeed, mutations in genes associated with the PIWI/piRNA pathway results in de-repression of TEs in the germline and leads to defects in development. (24)

The PIWI/piRNA pathway uses piRNA loaded on an argonaute protein called PIWI, to repress transcripts with repeats such as TEs. The pathway includes the loading of a single-stranded 26-30 nucleotides piRNA on a PIWI protein. (20) The loading requires the presence of the chaperone Hsp90 and of Shu a co-chaperone. (25, 26) Once the loading is completed, the piRNA and PIWI form the RNA-induced silencing complex (RISC). The RISC binds to target mRNA, creating a double stranded RNA between the target mRNA and piRNA. The formation of a double stranded RNA acts as a signal for the recruitment of various nucleases. The nucleases then proceed with the degradation of the target mRNA.

The PIWI/piRNA pathway does not only mediate degradation of TEs' transcripts but also promotes epigenetic silencing of TEs' coding sequence. (27) For instance, binding of the RISC complex to piRNA complementary DNA sequence, triggers epigenetic modifications such as histone acetylation and DNA methylation. Mechanisms involved in silencing of TEs similar to the PIWI/piRNA pathway, can be found in plants (28-30) and in yeasts. (31, 32) In plants it is called RNA directed methylation (RdDM) and in yeasts RNA-induced transcriptional silencing, both use siRNA instead of piRNA. Overall, RNAi mechanisms across organisms are responsible for degradation of TE transcripts and initiation of epigenetic silencing of TE sequences.

DNA Methylation

One of the epigenetic repression mechanisms triggered by RNAi is DNA methylation. DNA methylation is characterized by the addition of a methyl group on the 5th position of the cytosine ring (5-mC). The methylation of cytosine is widespread in CpG rich regions, which are prevalent in promoters and TEs. As a matter of fact, TEs constitute 40% of the CpGs in the human genome and are largely hypermethylated. (33) 5-mC is mostly associated with gene and TE repression by hindering the binding of transcription factors. (34) In the maize plant, DNA holo-methylation inhibits the Ac transposase binding to TEs. (35) Additionally, 5-mC initiates histone modification and heterochromatin formation through the binding of Methyl-DNA binding proteins (MBDs). (33) It is important to note that DNA methylation is not an invariable process across eukaryotes. For instance, DNA methylation in D.melanogaster is restricted to the embryonic development stage and is absent in the other life-stages. (36)

Histone Modification

Histones are the linking unit between DNA methylation and chromatin structure. Several types of histones exist (Histone, 1, 2A, 2B, 3, 4). Specific histones combine into octamers and form the nucleosome which is the fundamental unit of chromatin structure. (37) The state of the chromatin structure depends on the electric charge carried by the histones making up the nucleosome and on modified histone structures recognized by effector and reader proteins. (38) In their default state, histones are positively charged and interact tightly with DNA, forming a compact structure called heterochromatin, which often surrounds TEs sequences. However, histones and their electric charge can be altered in many different ways. For example, acetylation of histone tails neutralizes the positive charge and suppresses the electromagnetic interaction between histones and DNA, loosening the chromatin structure and releasing sequences from repression. Some histones, such as histone 1 (H1), are not part of the nucleosome. Yet, H1 is also involved in TE silencing. H1 interacts with methylated DNA sequences in active regions of the genome. (39) The interaction enhances the repression of TEs localized near genes, without promoting heterochromatin formation. (39)

We have now presented the principal eukaryotic systems tasked to silence TEs. Nevertheless, these basic defense systems did not prevent species to evolve additional silencing pathways to control TEs. Of particular interest, the repeat induced point (RIP) mutation system evolved by the fungi genus Neurospora, which in the case of N. crassa has led to the definitive silencing of all TEs. (40) RIP works by efficiently detecting and mutating both copies of a sequence duplication. Furthermore, RIP mutated sequences are also targeted for DNA methylation ensuring the complete silencing of TEs. (41)

How stress allows TEs to escape repressing pathways

It is now evident that genomes evolved an effective defense mechanism to prevent the spread of mobile elements. Yet, TE activity is regularly witnessed and appears to increase with stress. (16) In this part we will see that there are two ways TEs take advantage of stress to escape repressing mechanisms. The first one is the acquisition of stress responsive elements allowing them to be activated by stress related factors. The second is through the incapacitation of the silencing mechanism following stressful events. Although TE stress-induced activation is a widespread phenomenon it cannot be generalized to all transposons nor all organisms.

TEs with stress responsive elements

TEs equipped with responsive elements in their coding sequences have the ability to respond to the environment. For instance, ONSEN, a copia-like retrotransposon in Arabidopsis thaliana, possesses a heat-responsive element. (42, 43) Under heat stress conditions, the plant produces heat-stress defense factors (mostly transcription factors), which recognize and interact with the ONSEN heat responsive element. The interaction leads to the de-repression of ONSEN and favors its activation. (42) The presence of the heat-responsive element makes it impossible for the plant to respond to stress without losing control over ONSEN.

ONSEN is not the only known TE responding to variation in temperature. Tam3 is a TE present in snap dragons and is characterized by a transposase sensible to temperature, which is only activated under cold conditions. (44) Indeed, the transposase is only capable of binding a motif on the TE at temperatures around 15 degrees. The transposase binding on the motif causes Tam3 to be demethylated and is followed by its transposition. (44)

Temperature is not the only source of stress TEs can respond to. Tnt1 is a superfamily of LTR-retrotransposons, found throughout the Solanaceae plant family. It is activated by plant microbial factors ensuing a bacterial infection. (45) In the case of Tnt1, its activation allows it to spread both vertically through the host genome and horizontally through transposition in the bacterial genome. Some TEs such as Bare1 and FaRE1 in plants respond to Abscisic Acid (ABA), a hormone associated with stress response. (46, 47) This was elegantly shown by fusing a GUS protein to FaRE1 and monitoring GUS signal after administration of ABA. (47) Stress-responsive elements are diverse and common among TEs, it is hypothesized that they confer a competitive advantage against TEs lacking responsive elements in terms of transposition rate. (48)

Opportunistic TEs and impact of stress on silencing mechanisms

The possession of a regulatory element sensible to environmental cues is not the only way for TEs to be activated by stress. There is now evidence that TEs take advantage of silencing mechanisms downturn following stress. Indeed, it appears that cellular stress response and TE silencing mechanisms are antagonistic. This is illustrated with the dual role of Hsp90. We saw earlier that Hsp90 is required for the loading of piRNA on PIWI. (25) However, Hsp90 also plays an important role as a chaperone and in cellular physiological stress response. (49, 50) As such, when exposed to stress, Hsp90 prioritizes its role in cellular stress-response and

temporarily drops its activity in the piRNA/PIWI silencing pathway. (51) Hence, Hsp90 manifold roles are responsible for the downturn of the piRNA/PIWI pathway and the subsequent activation of TEs during stress.

Hsp90 is not the only protein impaired by its different roles in the presence of stress. KAP1 and SIRT6 are chromatin remodeling proteins involved in the formation of heterochromatin and silencing of TEs. (52) However, under stress conditions and during aging, SIRT6 and KAP1 are recruited to DNA breaks, which releases TEs from their repression. (53) In the absence of SIRT6 and KAP1 chromatin around TEs is no longer compacted, which facilitates TE activation. (52) Once more, it is the competing roles of a single protein that compromises TEs silencing mechanisms. The existence of competing roles for proteins often underlies the rapid re-purposing of an existing gene under an evolutionary pressure, where the duplication and emergence of a new gene fulfilling that advantageous function was not rapid enough. (54)

An alternative hypothesis is that a protein's competitive role evolved because TEs activation are beneficial to organisms under stress. Indeed, in some instances, it appears that cells are forced to impede repressing mechanisms enforced on TEs. Under stress conditions, Hsp70, an inducible chaperone, forms a complex with Hsp90 along with other factors involved in piRNA biogenesis. The complex is then targeted for degradation by the lysosome. (55) This results in the functional collapse of the piRNA/PIWI pathway and is followed by activation of TEs. (55) This study demonstrates that TE repression is loosened under stress conditions with the presence of Hsp70. Similarly, it is observed in plants, where demethylation of TE rich regions is naturally triggered by stress. (56) As such, it appears that loosening TE repression during stress episodes is an advantageous trait. The effect of these mechanisms occurring in germ cells, is to increase and generate genetic diversity, providing material for natural selection and evolution.

All organisms are regularly exposed to stress. Since stress appears to incapacitate repressing mechanisms, TEs should be proliferating in genomes. Yet, TE movement is overall low in most organisms. (57) One explanation is that relaxation of silencing mechanisms is insufficient for TE activation. This is the case with ONSEN, where stress-induced demethylation is not enough to induce its activation. (42) Another explanation is that stress does not activate all TEs, some are even repressed. (53) For example, in the rat's hippocampus, acute stress results in an increase of H3K9me3 (a histone mark associated with heterochromatin), which provokes a reduction in TE movement. (58) A strengthening of repressing mechanisms enforced on TEs is also witnessed in rice after phosphate starvation. (59) In rice, phosphate starvation results in an increase of 5mC around known TEs. (59) Thus, stress does not always incapacitate silencing pathways and does not always compromise germ cells integrity.

Finally, we have to keep in mind that TE activation is dependent on many factors such as location, type of TE, epigenetics, physiological state, cell type and cell cycle phase. For example, in a fungal pathogen, families of TEs show temporal variation in activation upon exposure to an identical stress. (60) Additionally, change in the fungal pathogen physiological state altered the TE activation pattern. Hence, TE stress-induced activation is hard to predict and cannot be generalized.

Outcomes of TE stress-induced activation

In this part, we will explore the wide range of consequences TE movement has on genomes. Additionally, we will investigate the impact TEs have on species' evolutionary history. As we will see, TE activation produces a lot of genetic variability. To the point, where they might be responsible for adaptive radiations. Finally, we will see that TEs are essential for populations' survival on the evolutionary timescale.

Repercussion of TE movement on genomes

Novel TE insertion near a gene leads to many outcomes (Figure 1.). A TE can modify a gene by disrupting its coding sequence. For instance, genes can be rendered non-functional with an insertion in the open reading frame (I.a) or by interfering with promoters/enhancers (I.c) However, new insertions may also be source of variability, with the incorporation of a new exon (a process called exonization) (I.e) (61), the modification of a transcription start site (I.g) (62), or the formation of a new polyadenylation site (I.b). (63) In addition to generating new exons, TEs can influence the splicing pattern of a gene (I.h). (64) This often happens with the addition of a splice site or by making two or more exons incompatible. We saw in the previous part, that TEs can be equipped with regulatory sequences. As a consequence, the novel insertion of a TE may introduce new cis-regulatory sites next to a gene and modify its expression pattern (I.d). For instance, a study demonstrated that ONSEN insertions resulted in up-regulation of downstream genes, contributing to the formation of an ABA insensitive phenotype. (65)

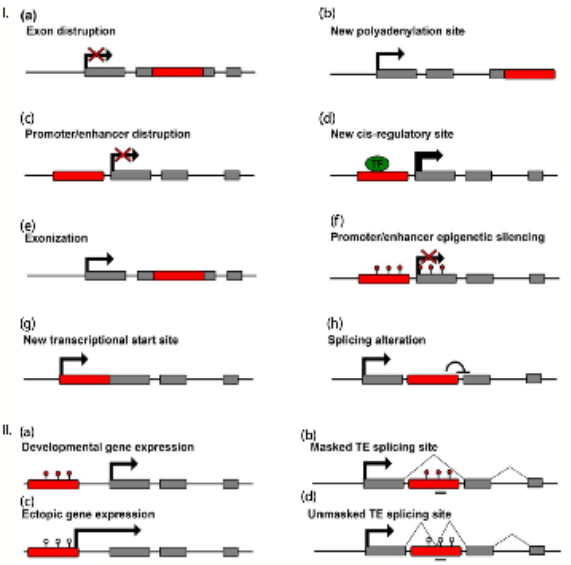

Figure 1. Schematic illustration of the various direct (I.) and indirect effects (II.) TEs have on genes. Red boxes represent newly inserted TE, grey boxes represent gene's open reading grame, red lollipops represent methylated DNA sites and white lollipops represent unmethylated sites. Black arrows represent transcription start site. a&b should write disruption. Figure from Pimpinelli, S and piacentini, L (92).

TEs do not necessarily have to be inserted in the coding region to affect gene expression. Indeed, TE insertion generating local epigenetic change is sufficient to impact gene expression. For example, TE insertion can result in local demethylation, unmasking cryptic promoters (II. C) and splice sites (II.d). Conversely, TE insertion can locally increase methylation, altering gene expression (II.a) and masking splice sites (II.b).

New TE insertions can influence the genome's architecture and chromatin state. Indeed, some TE families possess CTCF binding sites, which serve as anchor points for chromatin loops. (66) Hence, TEs introducing new CTCF binding sites induce divergent chromatin looping, re-shaping enhancer-promoter interactions and ultimately leading to altered gene expression. (67) There are other ways for TEs to influence the genome and gene expression. For instance, it is possible for TE to excise a complete gene and move it to a different genomic environment, resulting in a new gene expression profile. (68) Finally, the activation of Class II transposable elements, which generate a double strand break, is known to favor chromosomal rearrangements. (69) All in all, TEs have the power to modify the genome in a large number of ways and on different scales.

Sometimes, a TE produces a beneficial phenotype and the accountable insertion is conserved. This process is called TE exaptation. It describes the integration and conservation of TE insertions producing a beneficial phenotype. (70) Many genes originate from exapted TEs. For example, the

RAG genes, involved in the generation of antigen receptor repertoire in vertebrate's adaptive immune system, are derived from TEs. (71) Exapted elements are also embedded in regulatory networks. This is the case of FHY3 and FAR1, two transcription factors involved in the regulation of the photoreceptor phyA. (72) Interestingly, FAR1 emerged from a TE in the Mutator-like elements (MULEs) family. Elements in this family are periodically activated by stress. (73) It supports the hypothesis that stress facilitates and accelerates the creation of novel phenotypes. Recent studies showed that TEs insertions - called polymorphic mobile elements insertions (pMEIS) - were responsible for isoform diversity and differential gene regulation between human tissues. (74, 75)

TE activation is itself a source of stress that genomes have to face. As we saw previously some TE repression systems, such as RNAi, evolved under the threat of TE spread. (19) On one side, genomes and organisms are selected for their capacity to limit the stress imposed by transposable elements, which in turn forces TE to evolve systems to evade the silencing mechanisms. This could be compared to an evolutionary arms race between genomes and TEs. Yet, as we will see, it seems that TE activity is still required and needed to fuel genetic innovations on which populations are reliant on. Thus, in reality, genomes and TEs have reached a negotiated settlement, mutually depending on the others' existence.

TEs, a source of genetic diversity for populations

TE activity has the power to transform the genome on a small and large scale, but how important are TEs as a source of variation? For instance, could TE movement create enough genetic diversity to drive speciation? In diatoms, TEs are functionally involved in temperature stress response. The difference in TE insertions and families among diatom populations resulted into differential physiological response to stress. (76) In this case, TE movement could be the first step toward the speciation of diatom populations.

An emerging view called the TE-Thrust hypothesis (77), suggests that TE activation is responsible for adaptive radiations and evolution of lineages. (78) In fact, there is evidence to support that TE activity is linked to speciation events in mammals (79), angiosperms (80) and certain reptiles. (81) Moreover, primates adaptive radiation coincide with a burst in TE activity. (82) During such evolutionary events, stress might be responsible for triggering bursts in TE activity. For example, in the invasive species Cardiocondyla obscurior a large increase in TE movement is observed following founding events. (83) Founding events are known to put a lot of stress on the starting population as it needs to rapidly adapt to a new environment. TE burst could provide a molecular mechanism to Stress-Induced Evolutionary Innovation (SIEI), where sustained stress cues drive the formation of new group of cells - that characteristically exhibit more cellular stress - promoting the modelling and differentiation of new tissues. (84) Hence, there is increasing evidence to support the importance of TE stress-induced activation in the evolution of lineages and species. It would be interesting to monitor the rate of TE activity in endangered species to see if climate change related stress translates into higher TE activity and differential activation rate between populations.

Another argument advocates for the role of TEs in evolution. Can lineages persist on large timescales without TE activity? TEs are present in all eukaryotes and in most prokaryotes. Moreover, practically all studied organisms exhibit at least minimal TE activity. (85, 86) In fact, N. crassa is the only known living organism to have completely silenced TE activity with its RIP system. (40) It demonstrates that, first it is possible for evolution to produce systems that completely silence TEs and second, such systems are extremely rare and/or not conserved. Thus, suppression of TE activity appears to be an evolutionary dead-end. As a matter of fact, insufficient TE activity and lack of genetic variation might be responsible for extinctions among the sphenodontidae, a reptilian lineage. (78, 87) Hence, the conservation of TEs activity in almost all organisms indicates that TEs are essential for adaptation.

The TE-Thrust hypothesis only holds true if TE movement is not chaotic and completely uncontrolled. Indeed, TE movement is by itself a source of stress for genomes and organisms, illustrated by TEs implication in some human diseases such as monogenic disease allele, cancers and autoimmunity. (88, 89) If this source of stress becomes too intense under certain conditions, the affected population faces a risk of extinction. (90, 91) As such, the presence of repressing mechanisms and the idea of negotiated settlement is essential.

Conclusion

Genomes evolved a set of systems to prevent chaotic TE movement. However, the tools employed by genomes are not infallible. It appears that genomes and evolution tolerate and benefit from intrinsic flaws among silencing systems in order to facilitate TE activation when under stress. This is well illustrated with Hsp70 and the competing roles of silencing proteins. Moreover, some TEs borrowed stress-responsive elements to promote their own activation under stress. This widespread capacity to mobilize under stress indicates that TE stress-induced activation is necessary for populations to persist through time. As a matter of fact, increasing evidence supports the claim that TEs are important drivers of evolution and played a vital role in major adaptive radiations. All in all, TE stress-induced activation creates genetic variation, which fuels adaptation and speciation.

Acknowledgements

I would like to thank Professor Bureau for giving me the opportunity to write this review as a part of the BIOL 377 course. I also wish to express my gratitude to Nancy Nelson, who, through her invaluable advice, made my journey at McGill University a very pleasant and formative one. Overall, I wish to thank the professors that gave me the opportunity to hone my science, social and communication skills during my 3 years at McGill, thank you Prof. Hastings, Prof. Nepveu and Prof. Pavelka.

References

1. Index. In: Tollefsbol TO, editor. Handbook of Epigenetics (Second Edition): Academic Press; 2017. p. 653-68.

2. Handy DE, Castro R, Loscalzo J. Epigenetic modifications: basic mechanisms and role in cardiovascular disease. Circulation. 2011;123(19):2145-56.

3. Prakash V, Devendran R, Chakraborty S. Overview of plant RNA dependent RNA polymerases in antiviral defense and gene silencing. Indian Journal of Plant Physiology. 2017;22(4):493-505.

4. McClintock B. The origin and behavior of mutable loci in maize. Proc Natl Acad Sci U S A. 1950;36(6):344-55.

5. Wicker T, Gundlach H, Spannagl M, Uauy C, Borrill P, Ramírez-González RH, et al. Impact of transposable elements on genome structure and evolution in bread wheat. Genome Biology. 2018;19(1):103.

6. Yanchinski S. DNA - IGNORANT, SELFISH AND JUNK. New Sci. 1981;91(1262):154-5.

7. Dawkins R. The selfish gene: New edition. Oxford ; New York : Oxford University Press, 1989.; 1989.

8. McClintock B. The significance of responses of the genome to challenge. Science. 1984;226(4676):792.

9. Biemont C. A brief history of the status of transposable elements: from junk DNA to major players in evolution. Genetics. 2010;186(4):1085-93.

10. Wayne G. Rostant NW, David J. Hosken. Transposable elements and Insecticide Resistance. Advances in Genetecis. 2012;78:169-201.

11. Villasante A, Abad JP, Planelló R, Méndez-Lago M, Celniker SE, de Pablos B. Drosophila telomeric retrotransposons derived from an ancestral element that was recruited to replace telomerase. Genome Res. 2007;17(12):1909-18.

12. Jangam D, Feschotte C, Betrán E. Transposable Element Domestication As an Adaptation to Evolutionary Conflicts. Trends in Genetics. 2017;33(11):817-31.

13. Pimpinelli S, Piacentini L. Environmental change and the evolution of genomes: Transposable elements as translators of phenotypic plasticity into genotypic variability. Functional Ecology. 2020;34(2):428-41.

14. Chuong EB, Elde NC, Feschotte C. Regulatory activities of transposable elements: from conflicts to benefits. Nat Rev Genet. 2017;18(2):71-86.

15. Wicker T, Sabot F, Hua-Van A, Bennetzen JL, Capy P, Chalhoub B, et al. A unified classification system for eukaryotic transposable elements. Nature Reviews Genetics. 2007;8(12):973-82.

16. Liu B, Wendel JF. Retrotransposon activation followed by rapid repression in introgressed rice plants. Genome. 2000;43(5):874-80.

17. De Felice B, Wilson RR, Argenziano C, Kafantaris I, Conicella C. A transcriptionally active copia-like retroelement in Citrus limon. Cell Mol Biol Lett. 2009;14(2):289-304.

18. Hua-Van A, Le Rouzic A, Boutin TS, Filée J, Capy P. The struggle for life of the genome's selfish architects. Biol Direct. 2011;6:19-.

19. Obbard DJ, Gordon KHJ, Buck AH, Jiggins FM. The evolution of RNAi as a defence against viruses and transposable elements. Philosophical Transactions of the Royal Society B: Biological Sciences. 2009;364(1513):99-115.

20. Das PP, Bagijn MP, Goldstein LD, Woolford JR, Lehrbach NJ, Sapetschnig A, et al. Piwi and piRNAs Act Upstream of an Endogenous siRNA Pathway to Suppress Tc3 Transposon Mobility in the Caenorhabditis elegans Germline. Mol Cell. 2008;31(1):79-90.

21. Brennecke J, Aravin AA, Stark A, Dus M, Kellis M, Sachidanandam R, et al. Discrete small RNA-generating loci as master regulators of transposon activity in Drosophila. Cell. 2007;128(6):1089-103.

22. Aravin AA, Sachidanandam R, Girard A, Fejes-Toth K, Hannon GJ. Developmentally Regulated piRNA Clusters Implicate MILI in Transposon Control. Science. 2007;316(5825):744.

23. Carmell MA, Girard A, van de Kant HJ, Bourc'his D, Bestor TH, de Rooij DG, et al. MIWI2 is essential for spermatogenesis and repression of transposons in the mouse male germline. Dev Cell. 2007;12(4):503-14.

24. Klattenhoff C, Theurkauf W. Biogenesis and germline functions of piRNAs. Development. 2008;135(1):3.

25. Izumi N, Kawaoka S, Yasuhara S, Suzuki Y, Sugano S, Katsuma S, et al. Hsp90 facilitates accurate loading of precursor piRNAs into PIWI proteins. Rna. 2013;19(7):896-901.

26. Olivieri D, Senti K-A, Subramanian S, Sachidanandam R, Brennecke J. The cochaperone shutdown defines a group of biogenesis factors essential for all piRNA populations in Drosophila. Mol Cell. 2012;47(6):954-69.

27. Huang XA, Yin H, Sweeney S, Raha D, Snyder M, Lin H. A major epigenetic programming mechanism guided by piRNAs. Dev Cell. 2013;24(5):502-16.

28. Wierzbicki AT, Haag JR, Pikaard CS. Noncoding Transcription by RNA Polymerase Pol IVb/Pol V Mediates Transcriptional Silencing of Overlapping and Adjacent Genes. Cell. 2008;135(4):635-48.

29. Gao Z, Liu H-L, Daxinger L, Pontes O, He X, Qian W, et al. An RNA polymerase II- and AGO4-associated protein acts in RNA-directed DNA methylation. Nature. 2010;465(7294):106-9.

30. Wendte JM, Pikaard CS. The RNAs of RNA-directed DNA methylation. Biochimica et Biophysica Acta (BBA) - Gene Regulatory Mechanisms. 2017;1860(1):140-8.

31. Grewal SI. RNAi-dependent formation of heterochromatin and its diverse functions. Curr Opin Genet Dev. 2010;20(2):134-41.

32. Zofall M, Grewal SI. RNAi-mediated heterochromatin assembly in fission yeast. Cold Spring Harb Symp Quant Biol. 2006;71:487-96.

33. Edwards JR, Yarychkivska O, Boulard M, Bestor TH. DNA methylation and DNA methyltransferases. Epigenetics Chromatin. 2017;10:23.

34. Choy M-K, Movassagh M, Goh H-G, Bennett MR, Down TA, Foo RSY. Genome-wide conserved consensus transcription factor binding motifs are hyper-methylated. BMC Genomics. 2010;11:519-.

35. Ros F, Kunze R. Regulation of activator/dissociation transposition by replication and DNA methylation. Genetics. 2001;157(4):1723-33.

36. Lyko F, Ramsahoye BH, Jaenisch R. DNA methylation in Drosophila melanogaster. Nature. 2000;408(6812):538-40.

37. White CL, Suto RK, Luger K. Structure of the yeast nucleosome core particle reveals fundamental changes in internucleosome interactions. The EMBO Journal. 2001;20(18):5207-18.

38. Allshire RC, Madhani HD. Ten principles of heterochromatin formation and function. Nat Rev Mol Cell Biol. 2018;19(4):229-44.

39. Choi J, Lyons DB, Kim MY, Moore JD, Zilberman D. DNA Methylation and Histone H1 Jointly Repress Transposable Elements and Aberrant Intragenic Transcripts. Mol Cell. 2020;77(2):310-+.

40. Galagan JE, Calvo SE, Borkovich KA, Selker EU, Read ND, Jaffe D, et al. The genome sequence of the filamentous fungus Neurospora crassa. Nature. 2003;422(6934):859-68.

41. Gladyshev E. Repeat-Induced Point Mutation and Other Genome Defense Mechanisms in Fungi. Microbiol Spectr. 2017;5(4).

42. Cavrak VV, Lettner N, Jamge S, Kosarewicz A, Bayer LM, Mittelsten Scheid O. How a Retrotransposon Exploits the Plant's Heat Stress Response for Its Activation. PLOS Genetics. 2014;10(1):e1004115.

43. Matsunaga W, Kobayashi A, Kato A, Ito H. The effects of heat induction and the siRNA biogenesis pathway on the transgenerational transposition of ONSEN, a copia-like retrotransposon in Arabidopsis thaliana. Plant and Cell Physiology. 2011;53(5):824-33.

44. Hashida S-N, Uchiyama T, Martin C, Kishima Y, Sano Y, Mikami T. The temperature-dependent change in methylation of the Antirrhinum transposon Tam3 is controlled by the activity of its transposase. Plant Cell. 2006;18(1):104-18.

45. Grandbastien MA, Audeon C, Bonnivard E, Casacuberta JM, Chalhoub B, Costa AP, et al. Stress activation and genomic impact of Tnt1 retrotransposons in Solanaceae. Cytogenet Genome Res. 2005;110(1-4):229-41.

46. Vicient CM, Jääskeläinen MJ, Kalendar R, Schulman AH. Active retrotransposons are a common feature of grass genomes. Plant Physiol. 2001;125(3):1283-92.

47. He P, Ma Y, Dai H, Li L, Liu Y, Li H, et al. Characterization of the Hormone and Stress-Induced Expression of FaRE1 Retrotransposon Promoter in Strawberry. Journal of Plant Biology. 2012;55(1):1-7.

48. Abrusan G, Krambeck HJ. Competition may determine the diversity of transposable elements. Theor Popul Biol. 2006;70(3):364-75.

49. Erlejman AG, Lagadari M, Toneatto J, Piwien-Pilipuk G, Galigniana MD. Regulatory role of the 90-kDa-heat-shock protein (Hsp90) and associated factors on gene expression. Biochim Biophys Acta. 2014;1839(2):71-87.

50. Sangster TA, Lindquist S, Queitsch C. Under cover: causes, effects and implications of Hsp90-mediated genetic capacitance. Bioessays. 2004;26(4):348-62.

51. Ryan CP, Brownlie JC, Whyard S. Hsp90 and physiological stress are linked to autonomous transposon mobility and heritable genetic change in nematodes. Genome Biology and Evolution. 2016;8(12):3794-805.

52. Van Meter M, Kashyap M, Rezazadeh S, Geneva AJ, Morello TD, Seluanov A, et al. SIRT6 represses LINE1 retrotransposons by ribosylating KAP1 but this repression fails with stress and age. Nat Commun. 2014;5:5011.

53. Horváth V, Merenciano M, González J. Revisiting the Relationship between Transposable Elements and the Eukaryotic Stress Response. Trends in Genetics. 2017;33(11):832-41.

54. Copley SD. An evolutionary perspective on protein moonlighting. Biochem Soc Trans. 2014;42(6):1684-91.

55. Cappucci U, Noro F, Casale AM, Fanti L, Berloco M, Alagia AA, et al. The Hsp70 chaperone is a major player in stress-induced transposable element activation. Proceedings of the National Academy of Sciences. 2019;116(36):17943.

56. Liu R, Lang Z. The mechanism and function of active DNA demethylation in plants. Journal of Integrative Plant Biology. 2020;62(1):148-59.

57. Laricchia KM, Zdraljevic S, Cook DE, Andersen EC. Natural Variation in the Distribution and Abundance of Transposable Elements Across the Caenorhabditis elegans Species. Mol Biol Evol. 2017;34(9):2187-202.

58. Hunter RG, Murakami G, Dewell S, Seligsohn Ma, Baker MER, Datson NA, et al. Acute stress and hippocampal histone H3 lysine 9 trimethylation, a retrotransposon silencing response. Proceedings of the National Academy of Sciences. 2012;109(43):17657.

59. Secco D, Wang C, Shou H, Schultz MD, Chiarenza S, Nussaume L, et al. Stress induced gene expression drives transient DNA methylation changes at adjacent repetitive elements. eLife. 2015;4:e09343.

60. Fouche S, Badet T, Oggenfuss U, Plissonneau C, Francisco CS, Croll D. Stress-Driven Transposable Element De-repression Dynamics and Virulence Evolution in a Fungal Pathogen. Mol Biol Evol. 2020;37(1):221-39.

61. Schmitz J, Brosius J. Exonization of transposed elements: A challenge and opportunity for evolution. Biochimie. 2011;93(11):1928-34.

62. Feschotte C. Transposable elements and the evolution of regulatory networks. Nat Rev Genet. 2008;9(5):397-405.

63. Lee JY, Ji Z, Tian B. Phylogenetic analysis of mRNA polyadenylation sites reveals a role of transposable elements in evolution of the 3'-end of genes. Nucleic Acids Res. 2008;36(17):5581-90.

64. Abascal F, Tress ML, Valencia A. Alternative splicing and co-option of transposable elements: the case of TMPO/LAP2α and ZNF451 in mammals. Bioinformatics. 2015;31(14):2257-61.

65. Ito H, Kim J-M, Matsunaga W, Saze H, Matsui A, Endo TA, et al. A Stress-Activated Transposon in Arabidopsis Induces Transgenerational Abscisic Acid Insensitivity. Scientific Reports. 2016;6(1):23181.

66. Holwerda SJB, de Laat W. CTCF: the protein, the binding partners, the binding sites and their chromatin loops. Philos Trans R Soc Lond B Biol Sci. 2013;368(1620):20120369-.

67. Diehl AG, Ouyang N, Boyle AP. Transposable elements contribute to cell and species-specific chromatin looping and gene regulation in mammalian genomes. Nature Communications. 2020;11(1):1796.

68. Berrada S, Fournier D. Transposition-mediated transcriptional overexpression as a mechanism of insecticide resistance. Molecular and General Genetics MGG. 1997;256(4):348-54.

69. Zhang J, Yu C, Krishnaswamy L, Peterson T. Transposable Elements as Catalysts for Chromosome Rearrangements. In: Birchler JA, editor. Plant Chromosome Engineering: Methods and Protocols. Totowa, NJ: Humana Press; 2011. p. 315-26.

70. Joly-Lopez Z, Bureau TE. Exaptation of transposable element coding sequences. Current Opinion in Genetics & Development. 2018;49:34-42.

71. Fugmann SD. The origins of the Rag genes--from transposition to V(D)J recombination. Semin Immunol. 2010;22(1):10-6.

72. Lin R, Ding L, Casola C, Ripoll DR, Feschotte C, Wang H. Transposase-derived transcription factors regulate light signaling in Arabidopsis. Science (New York, NY). 2007;318(5854):1302-5.

73. Tittel-Elmer M, Bucher E, Broger L, Mathieu O, Paszkowski J, Vaillant I. Stress-induced activation of heterochromatic transcription. PLoS genetics. 2010;6(10):e1001175-e.

74. Cao X, Zhang Y, Payer LM, Lords H, Steranka JP, Burns KH, et al. Polymorphic mobile element insertions contribute to gene expression and alternative splicing in human tissues. Genome Biol. 2020;21(1):185.

75. Goubert C, Zevallos NA, Feschotte C. Contribution of unfixed transposable element insertions to human regulatory variation. Philosophical Transactions of the Royal Society B: Biological Sciences. 2020;375(1795):20190331.

76. Pargana A, Musacchia F, Sanges R, Russo MT, Ferrante MI, Bowler C, et al. Intraspecific Diversity in the Cold Stress Response of Transposable Elements in the Diatom Leptocylindrus aporus. Genes. 2020;11(1):25.

77. Oliver KR, Greene WK. Transposable elements and viruses as factors in adaptation and evolution: an expansion and strengthening of the TE-Thrust hypothesis. Ecology and Evolution. 2012;2(11):2912-33.

78. Oliver KR, Greene WK. Transposable elements: powerful facilitators of evolution. BioEssays. 2009;31(7):703-14.

79. Ricci M, Peona V, Guichard E, Taccioli C, Boattini A. Transposable Elements Activity is Positively Related to Rate of Speciation in Mammals. J Mol Evol. 2018;86(5):303-10.

80. Oliver KR, McComb JA, Greene WK. Transposable Elements: Powerful Contributors to Angiosperm Evolution and Diversity. Genome Biology and Evolution. 2013;5(10):1886-901.

81. Feiner N. Accumulation of transposable elements in Hox gene clusters during adaptive radiation of Anolis lizards. Proc Biol Sci. 2016;283(1840):20161555.

82. Oliver KR, Greene WK. Mobile DNA and the TE-Thrust hypothesis: supporting evidence from the primates. Mobile DNA. 2011;2(1):8.

83. Schrader L, Kim JW, Ence D, Zimin A, Klein A, Wyschetzki K, et al. Transposable element islands facilitate adaptation to novel environments in an invasive species. Nature Communications. 2014;5(1):5495.

84. Wagner GP, Erkenbrack EM, Love AC. Stress-Induced Evolutionary Innovation: A Mechanism for the Origin of Cell Types. Bioessays. 2019;41(4):e1800188.

85. Vangelisti A, Mascagni F, Usai G, Natali L, Giordani T, Cavallini A. Low

Long Terminal Repeat (LTR)-Retrotransposon Expression in Leaves of the Marine Phanerogam Posidonia Oceanica L. Life-Basel. 2020;10(3):12.
86. Pace JK, 2nd, Feschotte C. The evolutionary history of human DNA transposons: evidence for intense activity in the primate lineage. Genome Res. 2007;17(4):422-32.

87. Wang Z, Miyake T, Edwards SV, Amemiya CT. Tuatara (Sphenodon) genomics: BAC library construction, sequence survey, and application to the DMRT gene family. J Hered. 2006;97(6):541-8.

88. Burns KH. Our Conflict with Transposable Elements and Its Implications for Human Disease. In: Abbas AK, Aster JC, Feany MB, editors. Annual Review of Pathology: Mechanisms of Disease, Vol 15, 2020. Annual Review of Pathology-Mechanisms of Disease. 15. Palo Alto: Annual Reviews; 2020. p. 51-70.

89. Lynch-Sutherland CF, Chatterjee A, Stockwell PA, Eccles MR, Macaulay EC. Reawakening the Developmental Origins of Cancer Through Transposable Elements. Front Oncol. 2020;10:15.

90. Rankin DJ, Bichsel M, Wagner A. Mobile DNA can drive lineage extinction in prokaryotic populations. J Evol Biol. 2010;23(11):2422-31.

91. Abascal F, Corvelo A, Cruz F, Villanueva-Canas JL, Vlasova A, Marcet-Houben M, et al. Extreme genomic erosion after recurrent demographic bottlenecks in the highly endangered Iberian lynx. Genome Biology. 2016;17:18.

92. Pimpinelli S, Piacentini L. Environmental change and the evolution of genomes: Transposable elements as translators of phenotypic plasticity into genotypic variability. Functional Ecology. 2020;34(2):428-41.