Trends in Genetics

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Review

Transposable Elements Direct The Coevolution between Plants and Microbes

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Transposable elements are powerful drivers of genome evolution in many eukaryotes. Although they are mostly considered as 'selfish' genetic elements, increasing evidence suggests that they contribute to genetic variability; particularly under stress conditions. Over the past few years, the role of transposable elements during host–microbe interactions has been recognised. It has been proposed that many pathogenic microbes have evolved a 'two-speed' genome with regions that show increased variability and that are enriched in transposable elements and pathogenicity-related genes. Plants similarly display structured genomes with transposable-element-rich regions that mediate accelerated evolution. Immune receptor genes typically reside in such regions. Various mechanisms have recently been identified through which transposable elements contribute to the coevolution between plants and their associated microbes.

Trends

Transposable elements are powerful drivers of adaptive genome evolution in plants and in symbiotic microbes, and contribute to their coevolution.

Analysis of large next-generation sequencing datasets fuels a better understanding of the precise role of transposable elements in genome evolution, revealing active as well as passive contributions.

Transposable elements contribute to genome evolution through diverse mechanisms, by mediating structural variations, gene inactivation, gene copy variation, but also by affecting gene expression.

Further mechanistic understanding of the role of transposable elements in genome evolution will come from detailed structural analysis of chromatin.

Transposable Elements: Drivers of Evolution

Evolution is a never-ending process in which genetic changes over successive generations allow biological populations to increase fitness in the environment in which they reside. However, most environments are dynamic and continuously subject to subtle or more significant changes. Plants need to adapt rapidly to changing environments since their mostly uncontrolled mechanisms of offspring dispersal and their inability to relocate after germination forces them to be able to also survive in less-well-suited habitats. In such habitats, plants may be exposed to multiple **abiotic stressors** (see Glossary), such as extreme temperatures, inappropriate water or mineral availability. Adaptation to such stresses is mediated by genetic variation, which can be established by a plethora of mechanisms ranging from single nucleotide polymorphisms to whole-genome duplications. Additionally, also **epigenetic** variation contributes to stress adaptation.

In many eukaryotes, **transposable elements** are powerful drivers of genome evolution [1–3]. Transposable elements are often considered 'selfish' genetic elements because they can autonomously jump within a genome, either through copy–paste (retrotransposon) or cut-and-paste (DNA transposon) mechanisms. Transposable element activity can considerably impact genome structure and function, for example, through gene disruption; through mediating genomic rearrangements that cause translocation, duplication or deletion of genetic material; or through affecting proximal gene expression [1–3]. Since excessive transposable element activity typically negatively impacts the fitness of an organism, their activity is generally suppressed by genome defence mechanisms such as **DNA methylation** [4,5]. Depending on their impact on fitness, transposable-element-induced mutations are purged from the population; the speed of which depends on the effective population size. Nevertheless, in particular

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cases, the genetic variability induced by a transposable element contributes to adaptive genome evolution. For example, a transposon insertion in the first intron of the *Arabidopsis thaliana FLOWERING LOCUS C* (*FLC*) leads to early flowering by overcoming the vernalisation requirement, thus impacting reproduction in particular environments [6–8]. Intriguingly, transposable elements whose activity is suppressed by genome defence mechanisms can become re-activated when plants are exposed to abiotic stressors [9], suggesting that transposable element mobilisation facilitates the establishment of the genetic variability that is required for adaptation.

Plants are not only subject to abiotic stress, but also to **biotic stress** incited by the interaction with pests and various types of microbes (Figure 1A). The **symbiosis** between plants and microbes ranges from mutualistic through commensalistic to parasitic. To respond to the various types of microbial invaders, plants evolved intracellular and extracellular immune receptors that recognise invasion and activate appropriate immune responses [10]. Microbes that are able to successfully initiate symbiosis secrete so-called **effectors** to establish their interaction, for instance, through deregulation of immune responses [11]. However, hosts typically evolved to intercept pathogen effectors with novel immune receptors to reinstate immunity and halt pathogen ingress [10,11]. To avoid or overcome such recognition, pathogens need to purge or modify these effectors, or evolve novel ones to suppress the reinstated immune response [11], leading to an everlasting coevolution between plants and their pathogens [10] (Figure 1A).

Over the past few years, the importance of transposable elements to establish genetic plasticity during host–microbe interactions has been recognised [3,12–14]. However, detailed studies on genome-wide transposable element distributions and mechanistic insights into their impact on adaptive genome evolution have been hampered in genomics studies as a direct consequence of the extreme abundance of transposable elements. Highly abundant, nested, and often degenerated transposable element copies typically obstruct high-quality genome assemblies, resulting in considerable fragmentation of transposable element-rich regions [15]. Recent technological advances such as long-read sequencing and the use of chromatin interaction maps to order genomic sequences along chromosomes facilitate the establishment of contiguous genome assemblies, which permits study of the impact of transposable elements on genome evolution [15,16]. Here, we discuss our most recent understanding of mechanisms by which transposable elements mediate genome variability in plant–microbe interactions, and how these drive coevolution.

Transposable Elements Contribute to Fungal Adaptation and Pathogenicity

Based on genome sequencing efforts during the past decade, it is now widely recognised that eukaryotic genomes are not just a random sequence of genes, but are highly structured with coexpressed genes or genes involved in similar biological processes physically clustered along chromosomes [17]. Moreover, also transposable elements are not randomly distributed, but often cluster in transposable element-rich regions (Figure 1B). Intriguingly, effector genes of many plant-associated microbes are located either within or in proximity to transposable element-rich regions [12–14,16] (Figure 1B). These observations gave rise to the hypothesis that many pathogenic microbes evolved a so-called 'two-speed' genome in which gene-rich and transposable-element-poor regions evolve slowly, while gene-poor and transposable-element-rich effector regions evolve rapidly [12,14]. Notably, depending on the organism, these transposable-element-rich genomic regions, which are presumed to evolve rapidly, are either embedded within the core chromosomes, or reside on conditionally dispensable chromosomes [18–25]. Due to the strong correlation between effector location and transposable element abundance, it has been proposed that transposable elements contribute to microbial adaptation by facilitating the swift evolution of effector-rich regions in response to plant

Glossary

Abiotic stressor: nonliving chemical or physical component of the environment that causes stress to a living organism.
AT isochore: part of a chromosome that displays elevated levels of the A and T nucleotides.
Biotic stressor: an organism in the environment that causes stress to another organism.
DNA methylation: a process by which methyl groups are added to a DNA molecule to change its activity.
Effector: a molecule secreted by a pathogen to facilitate host colonisation, often through deregulation of host immune responses.
Epigenetics: heritable changes in gene expression (phenotype) that does not involve direct changes to the underlying primary DNA sequence (genotype).
Eudicot: dicotyledonous flowering plants of which the seeds contain two embryonic leaves (cotyledons).
Heterochromatin: DNA that is tightly packed around protein complexes (histones) and therefore largely inaccessible.
Monocot: monocotyledonous flowering plants of which the seeds contain only one embryonic leaf (cotyledon).
Pericentromeric: the region surrounding the centromere of a chromosome.
Recombination: a genetic process by which a DNA strand is broken and joined to another DNA strand.
Retroduplication: a process, mediated by enzymes acquired from transposable elements (retrotransposons), in which processed mRNA is reverse transcribed into DNA that is integrated into the genome.
RIP: repeat-induced point mutation, a meiosis-associated fungal defence mechanism that actively induces point mutations in transposable elements.
Symbiosis: literally living together, and separated into mutualism (both partners benefit), commensalism (one partner benefits, the other one is harmed, not helped), and parasitism (one partner benefits at the expense of the other).
Transposable element: a DNA sequence that can change its position within a genome, divided into retrotransposons that function

immunity by establishing genetic variability [12,19,20,23–32], yet their precise role remains largely unknown [12–14]. Importantly, the direct effect of transposable elements on the actual speed of evolution remains largely obscure, as rates of adaptation *per se* have not been estimated properly for most pathogens to which a 'two-speed' genome organisation has been attributed.

via reverse transcription, and DNA transposons that encode a transposase that is required for insertion and excision.
Virulence: the degree of aggressiveness of a pathogen.

Some understanding of the contribution of transposable elements to genetic variability in plant–microbe interactions was obtained by studying the *Avr-Pita* effector of the rice blast fungus *Magnaporthe oryzae* that is recognised by the Pita immune receptor in rice [33]. Diversification by point mutations and genomic instability of *Avr-Pita* through deletion or insertion enables *M. oryzae* isolates to overcome Pita-mediated resistance [33,34]. Notably, *Avr-Pita* resides in a subtelomeric region and is flanked by transposable elements, suggesting that its genomic instability may be associated with the surrounding transposable elements [33,35]. Indeed, insertion of a transposable element in the *Avr-Pita* promoter region results in gain of **virulence** on Pita plants [36] (Figure 1C). Moreover, transposable elements flanking *Avr-Pita* are thought to mediate the frequent loss of *Avr-Pita*, and also to contribute to the translocation of *Avr-Pita* between subtelomeric regions of different chromosomes between isolates [37] (Figure 1C). Notably, the transposable-element-mediated mobility of *Avr-Pita*, together with the exchange of genetic material between *M. oryzae* isolates, may cause the recovery of *Avr-Pita* in isolates that are no longer exposed to Pita-imposed selection pressure [37]. Likely, transposable elements are responsible for the frequent loss, gain, and translocation of other *M. oryzae* effectors as well [38].

Similar patterns of transposable-element-mediated gene loss and translocation have been observed in other fungal pathogens. For example, an effector gene located in proximity to a transposable element cluster in the wheat pathogen *Zymoseptoria tritici* was lost multiple times from the population, likely to avoid recognition by an unknown immune receptor [39]. Effector genes of *Leptosphaeria maculans*, the causal agent of stem canker on *Brassica*, localise in transposable-element-rich regions, referred to as **AT isochores**, that are subject to repeat-induced point mutation (**RIP**) [23]; a fungal defence mechanism against transposable elements that actively induces point mutations in duplicated sequences, leading to a local elevation of AT levels [40]. Effectors in these AT isochores can also be affected by 'leakage' of the RIP process from transposable elements into neighbouring sequences, leading to rapid effector diversification [41,42] (Figure 1C). *L. maculans* strains and their close relatives differ significantly in their transposable element content, ranging from 4% to 33%, and comparisons between *Leptosphaeria* species have revealed a recent transposable element expansion in the genome of *L. maculans* pathotype *brassicae* that contributes to the formation of the AT isochores [23,29]. It has been hypothesised that transposable elements likely contributed to the translocation of effectors into AT isochores [29]. Intriguingly, the genomes of the barley powdery mildew *Blumeria graminis* f.sp. *hordei* and of other powdery mildews display massive genome expansions that are correlated with retrotransposon proliferation, which may have been enabled due to the absence of an active RIP machinery in these genomes [43].

Abundant transposable elements and other repetitive sequences can foster large chromosomal rearrangements that may lead to translocation, duplication, or deletion of genetic material by acting as an ectopic substrate for double-strand break repair pathways [13]. In *Z. tritici*, nonallelic homologous **recombination** between transposable element copies located on sister chromatids has been implicated in large genomic insertions [44] (Figure 1C). In the soil-borne vascular wilt pathogen *Verticillium dahliae*, large chromosomal rearrangements have led to extensive chromosomal length polymorphisms between strains [24,25]. Comparisons of gapless genome assemblies of two *V. dahliae* strains with >99.9% nucleotide identity have revealed that these genomic rearrangements are most likely established by unfaithful double-

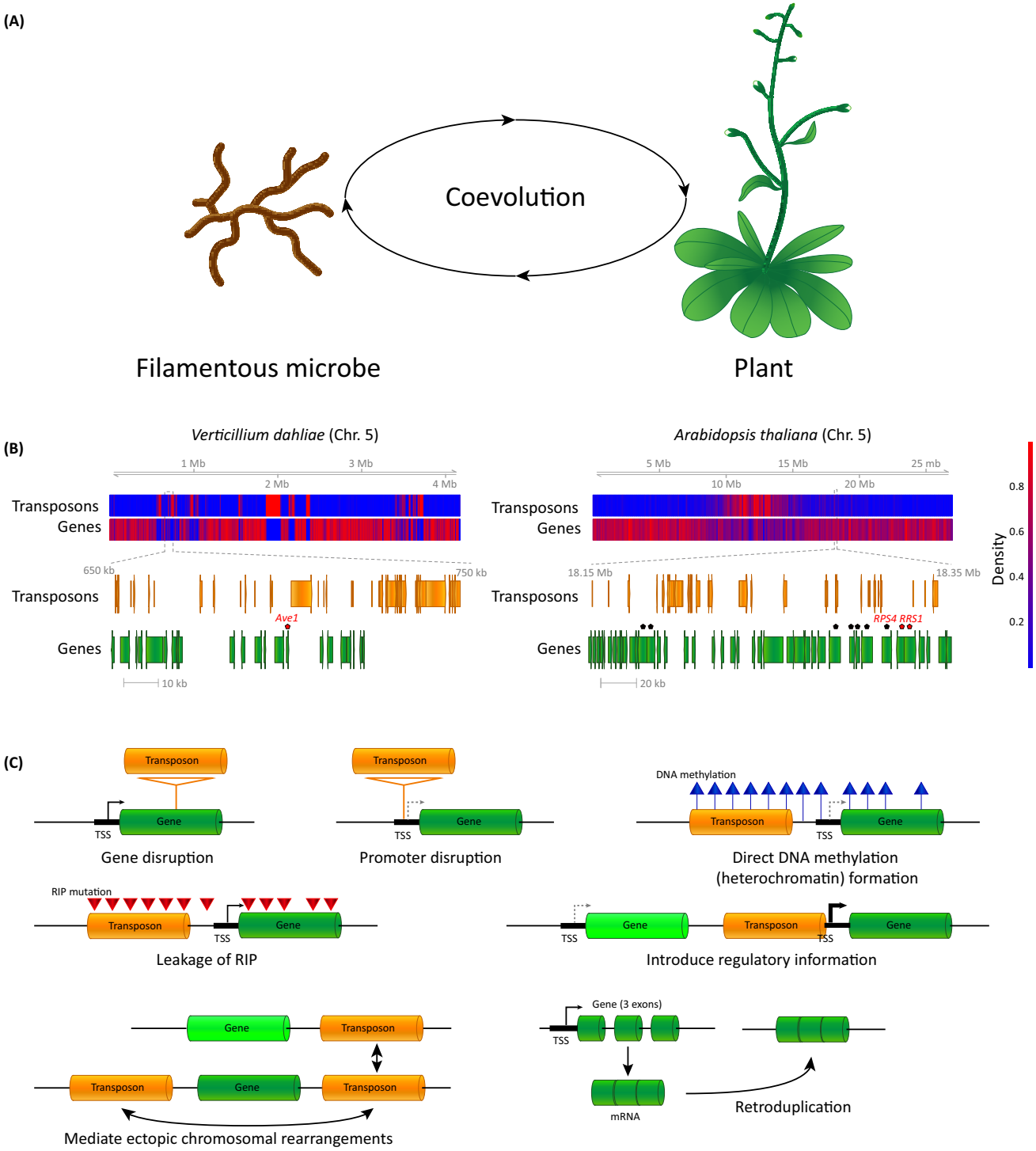

Figure 1. Transposable Elements Direct Coevolution between Plants and Microbes. (A) Plants and their associated microbes are engaged in coevolutionary arms races. (B) Genomes of plants and microbes typically have structured genomes with distinct transposable-element-rich regions that display accelerated evolution. The vascular wilt pathogen *Verticillium dahliae* has transposable-element-rich regions embedded in its chromosomes (here chromosome 5) that contain *in planta* induced effector genes such as *Ave1* [24,25,45]. Similarly, the genome of the thale cress *Arabidopsis thaliana* contains transposable-element-rich regions (exemplified by chromosome 5), strongly pronounced around the centromeres, but also around gene clusters that encode components of the plant immune system (e.g., the cluster

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strand break repair that utilises homologous sequences [25]. Thus, due to their abundance and sequence similarity, transposable elements frequently act as substrate for repair [25] (Figure 1C). The genomic rearrangements, in turn, contribute to the emergence of dynamic lineage-specific regions that are characterised by their high content of active transposable elements, recent segmental duplications, and frequent presence/absence polymorphisms between *V. dahliae* strains [24,25]. Intriguingly, these lineage-specific regions are not enriched for effector genes *per se*, but show enrichment for *in planta* induced effector genes; several of which have been shown to significantly contribute to *V. dahliae* virulence [24,45,46].

Similar as for *M. oryzae Avr-Pita*, transposable elements of *V. dahliae* have been implicated in overcoming host immunity. Resistance in tomato against *V. dahliae* is mediated by the cell surface receptor Ve1 that recognises the secreted *V. dahliae* effector Ave1 [45,47]. Intriguingly, no allelic variants of *Ave1* have been identified in the *V. dahliae* population, and resistance breaking strains consistently show loss of the *Ave1* gene that is flanked by transposable elements in strains that carry the effector gene (Figure 1B,C). Moreover, multiple independent losses of the *Ave1* effector gene have been recorded in the *V. dahliae* population [24,25,45]. Additionally, an insertion of a transposable element to inactivate an effector gene that is under diversifying selection has been observed (Figure 1C); potentially to avoid the activation of immunity in an unknown host plant by an unknown immune receptor (Thomma, *et al.*, unpublished).

Collectively, the studies discussed above, among others, suggest that transposable elements play a decisive role in plant–microbe interactions because they mediate accelerated evolution of microbial genomes. A deep mechanistic understanding of how transposable elements establish accelerated evolution is often still lacking. However, our recent work on the role of transposable elements in the evolution of *V. dahliae* has revealed active contributions, through transposable element activity, as well as passive contributions by acting as substrates for homology-based repair [25]. Such passive contributions are likely due to their abundance and high degree of sequence similarity.

To control the activity, and thus the spread, of transposable elements, in many fungal microbes, transposable-element-rich regions are highly condensed (**heterochromatin**), which is directed by DNA methylation in epigenetic regulation [4,5,48]. Heterochromatin formation is often not restricted to single genes but concerns larger regions, therefore, transposable elements can influence the expression of genes in their vicinity [48–52]. In the basidiomycete fungus *Pleurotus ostreatus*, for example, expression of genes flanked by transposable elements is significantly repressed. This was proposed to be driven by the spread of DNA methylation from transposable elements into neighbouring genes [53] (Figure 1C). In many plant-associated microbes, genes with important roles in establishment of symbiotic interactions are located in proximity to transposable elements, and their expression is controlled by heterochromatin [50,54,55] (Figure 1B,C). For example, expression of effector genes located in transposable-element-rich regions in the cereal pathogen *Fusarium graminearum* and in *L. maculans* is regulated by chromatin dynamics [50,54]. In the mutualistic fungus *Epichloë festucae*, two gene clusters responsible for the production of bioactive secondary metabolites that support symbiosis are located in transposable-element-rich, subtelomeric regions [55].

that contains the gene pair *RPS4/RRS1* [69]). Effector genes and immunity-related genes are marked with black pentagons, and *Ave1* as well as *RPS4/RRS1* are highlighted by red pentagons. (C) Transposable elements can contribute to genetic and transcriptomic variability by various mechanisms. Transposable elements can contribute to genetic variability by gene disruption, leakage of repeat induced point mutations (RIP) into neighbouring genes, or mediating large ectopic chromosomal rearrangements that can lead to translocations, inversions, duplications, or deletions. Similarly, transposable elements can contribute to the emergence of gene duplications by retroduplication, when processed mRNA is reverse-transcribed into DNA and subsequently re-integrated into the genome using enzymes acquired from retrotransposons. Additionally, transposable elements can contribute to transcriptomic variability by altering regulatory information through promoter disruption, by the introduction of ectopic regulatory information, as well as by directing the formation of DNA methylation and heterochromatin. Abbreviation: TSS, transcription start site

Interestingly, interaction between the fungus and its host leads to heterochromatin derepression, which leads to induction of the biosynthetic genes [55]. Similarly, secondary metabolite clusters in *F. graminearum* are located at subtelomeric transposable-element-rich heterochromatic regions [54]. Expression of these clusters is repressed *in vitro*, and mutations in enzymes involved in heterochromatin formation lead to derepression of many of these clusters [54]. Collectively, these examples suggest that proximity to transposable elements and specific manipulation of chromatin during the interaction between microbes and their hosts is a crucial factor to determine the expression of genes important for plant–microbe interactions [51,52,54,55].

Transposable Elements in Plants

Similar to the genomes of pathogenic fungi and other filamentous pathogens [12], the genomes of plant species differ significantly in their size and repeat content [56] (transposable elements, but also simple and tandem repeats), ranging from <20% of the *A. thaliana* genome and up to ~80% in cereals such as wheat and maize [57–59]. Chromosomes in the repeat-rich genomes of barley and bread wheat can be divided in three compartments (distal, interstitial, and proximal) that differ in the distribution of transposable elements with respect to age and type, in gene density and function, and in recombination frequency, suggesting that transposable elements play important roles in genome organisation and evolution [60–62]. However, the transposable element content differs between, as well as within, species. By comparing a subset of the recently sequenced 1135 *A. thaliana* genomes [63], several thousand transposable element insertion and deletion variants were identified [64,65]. The transposable element density increases at **pericentromeric** regions towards the centromeres, while gene density reduces in these regions [57] (Figure 1B); a pattern that is similarly observed in other plants such as wild rice [66]. Recent transposable element insertions in *A. thaliana* are uniformly distributed over all chromosomes, suggesting that transposable element insertions near genes along the chromosome arms often negatively affect fitness and are thus purged from the population [64,65]. While similar patterns are also observed in *Arabidopsis lyrata* [67], its genome is considerably larger than that of *A. thaliana* (207 versus 125 Mb), suggesting that recent transposable element proliferation in *A. lyrata* in combination with effective transposable element purging in *A. thaliana* played an important role in establishing the genome size difference [67]. Extensive transposable element proliferation, accompanied by reduced capacity to silence transposable element activity, strongly contributed to the 375-Mb genome size of *Arabis alpina*, a relative of both *A. thaliana* and *A. lyrata*, resulting in significantly larger pericentromeric regions with a large proportion of protein-coding genes [68]. Besides genome expansion, transposable elements have been associated with the majority of structural variations within the *Arabidopsis* population [69]. Comparisons between *A. thaliana* and *A. lyrata* have revealed large genomic rearrangements, with breakpoints enriched in transposable elements [67]. Similarly, comparisons between two rice species (wild and Asian rice) revealed ~200 inversions, of which the majority is flanked by transposable elements [66] (Figure 1C). Therefore, due to their abundance in plant genomes, transposable elements are generally considered important contributors to the formation of structural variations, for example, genome rearrangements, insertions, and deletions (Figure 1C).

Transposable elements in plant immunity

Genes encoding immune receptors can occur in single copies, but are often found in clusters both in **monocot** and in **eudicot** plant species. The evolution of such immune clusters is highly dynamic, as clusters display presence–absence polymorphisms, copy number variation, as well as frequent recombination [66,67,70,71]. Genes encoding immune receptors are often located in dynamic genomic regions. For example, defence-related genes in tomato, wheat, and barley are located in distal regions of the chromosomes that are characterised by high

recombination rates that contribute to diversification [61,62,72]. Moreover, in many plants these genes are flanked by transposable elements that also contribute to their evolution [65,69,71,73,74]. For example, expanded immune receptor gene families in grapevine and pepper evolved by duplications mediated by transposable elements [73,75]. Comparison of the immune receptor genes *L*, *I2*, and *R3a* that protect pepper against Tobamoviruses, tomato against *Fusarium oxysporum* f.sp. *lycopersici*, and potato against *Phytophthora infestans*, respectively, suggests that these genes evolved through transposable-element-mediated duplications [75] (Figure 1C). These immune receptors, and a considerable number of additional genes encoding nucleotide-binding and leucine-rich repeat-type immune receptors in pepper are encoded by single exon genes, while their respective ancestors are encoded by genes with multiple exons, suggesting that they evolved by **retroduplication** [75]. During this process, processed mRNA is reverse transcribed into DNA and subsequently, mediated by enzymes acquired from retrotransposons, integrated into the genome. The usage of an mRNA intermediate results in an intron-less descendent of the ancestral gene (Figure 1C). Many plant pathogen effector gene families have largely expanded through duplications, and effector genes generally do not contain introns, therefore, transposable-element-mediated retroduplication may play a role as well.

As a result of transposable element activity, immune receptors may also be lost in particular species or in a subset of a population, potentially to counter the fitness cost associated with their maintenance in the absence of a recognised microbial invader. Structural variations that are strongly associated with transposable elements in the *Arabidopsis* population are also enriched for defence-related genes, including those encoding immune receptors [69]. For example, the transposable element-rich immune receptor gene cluster that contains the gene pair *RPS4*/*RRS1* is highly variable between different *Arabidopsis* ecotypes, displaying insertions and deletions [69] that may be mediated by transposable elements (Figure 1B). However, adaptation to pathogens does not only occur through variation in the immune receptor gene clusters. The loss or mutation of genes encoding components required by microbial invaders to establish their symbiosis, so-called susceptibility genes, can provide immunity [76]. For example, the insertion of a transposable element in cucumber *MLO8* causes aberrant splicing (Figure 1C), leading to a loss-of-function mutation and immunity to fungal powdery mildew pathogens [77].

Transposable elements not only impact immune receptor repertoires, but also affect immune receptor gene expression directly, by influencing gene regulation, as well as indirectly, by affecting the local chromatin structure [65,69,78]. A transposable element insertion within an exon of the *A. thaliana* immune receptor gene *AtRLP18*, which confers resistance to the bacterial pathogen *Pseudomonas syringae*, is associated with a truncated transcript (Figure 1C) and leads to increased sensitivity towards *P. syringae* [65]. However, this transposable element insertion not only affects *AtRLP18*, but also leads to reduced expression of a neighbouring immune receptor gene [65]. Because of silencing of transposable elements by DNA methylation [4,5], recent transposable element insertions can thus lead to local changes in DNA methylation that can spread from the transposable element and thereby suppress the expression of nearby genes [64,65] (Figure 1C). Interestingly, transposable elements can be differentially methylated in response to biotic stresses, thereby dynamically modulating expression of neighbouring genes, including defence genes [79]. Remarkably, transposable element insertions not only lead to suppression of gene expression, due to local changes in DNA methylation, but also lead to elevated expression levels [65,80]. For example, a transposable element insertion near two *A. thaliana* genes resulted in increased expression of only one of them, suggesting that the transposable element may have carried directional regulatory information [65] (Figure 1C). Similarly, induction of gene expression in response to environmental (abiotic) stress was shown for a considerable number of maize genes with nearby

transposable element insertions, indicating that transposable elements contribute to their regulation [80]. Therefore, transposable elements provide a rich source of genetic and regulatory diversity between individuals (Figure 1C), thereby contributing to the adaptive evolution of their plant hosts to novel environments and to invading microbes.

Concluding remarks

Highly abundant and active transposable elements contribute significantly to the size and structure of the genomes of plants and their associated microbes (Figure 1B). Transposable elements drive genome and transcriptome variability by mediating structural variation and inciting alterations in gene expression due to modifications in the local chromatin landscape (Figure 1C), thereby contributing to the adaptation to changing environments. It is thus not surprising that transposable-element-mediated genome and transcriptome variability also fuels the everlasting arms races between plants and their microbial invaders (Figure 1A), irrespective of the type and lifestyle, as they mediate the rapid evolution of both components of the plant immune system and of microbial effector repertoires. However, so far, most studies into the contribution of transposable elements have been descriptive in nature, describing naturally occurring associations between transposable element occurrences and genome, transcriptome and phenotypic variations. A boost in our understanding of the mechanistic role that transposable elements play may come from the detailed analysis of chromatin structure, and in particular its 3D organisation within the nucleus, to reveal more precise mechanisms in structural genome variations (see Outstanding Questions). Finally, however, experimental evidence is required to directly show that specific modulation of transposable elements and their activities impacts adaptive genome evolution.

Outstanding Questions

Do transposable elements truly mediate accelerated evolution by affecting the rate of genetic variability in nearby genes?

How is the activity of transposable elements in the genome controlled, and how is this activity contained to specific compartments that require accelerated evolution?

What is the precise role of particular chromatin modifications in the containment of transposable element activity and adaptive genome evolution?

How does the 3D structure of chromatin in the nucleus contribute to the role that transposable elements play in adaptive genome evolution?

Does the 3D organisation of chromatin affect transposable element activity?

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