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Opinion

A devil's bargain with transposable elements in plant pathogens

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Transposable elements (TEs) spread in genomes through self-copying mechanisms and are a major cause of genome expansions. Plant pathogens have finely tuned the expression of virulence factors to rely on epigenetic control targeted at nearby TEs. Stress experienced during the plant infection process leads to derepression of TEs and concurrently allows the expression of virulence factors. We argue that the derepression of TEs elements causes an evolutionary conflict by favoring TEs that can be reactivated. Active TEs and recent genome size expansions indicate that plant pathogens could face long-term consequences from the short-term benefit of fine-tuning the infection process. Hence, encoding key virulence factors close to TEs under epigenetic control constitutes a devil's bargain for pathogens.

Highlights

Many filamentous pathogens have compartmentalized genomes with gene-rich and gene-poor regions where genes involved in virulence (i.e., effectors) are often located near TEs.

TEs govern the regulation of effector genes in TE-rich compartments through epigenetic effects. This enables tight regulatory timing with the plant infection but incurs long-term risks to host genome integrity. We refer to this as the devil's bargain of the plant pathogens.

TE activation can have drastic fitness consequences for the host, such as the disruption of essential genes and mediating chromosome rearrangements. TE activation can drive genome size expansions over evolutionary time.

The exact sequence of evolutionary events tying effector regulation and TEs remains poorly understood. Genomic surveys and epigenetic analyses have the potential to unravel causal mechanisms.

The tangled relationship between TEs and pathogen virulence

Transposable elements (**TEs**; see Glossary) are selfish genetic units that encode functions which facilitate their own proliferation in the genome. Through the creation of duplicated sequences, TEs mediate chromosome rearrangements and alter the expression landscape of nearby genes [1,2]. Uncontrolled proliferation of TEs increases the likelihood of deleterious rearrangements, leading to **genome instability** [3,4]. Consequently, most species have evolved defense mechanisms to prevent TE proliferation [1]. On the flip side, TEs are recognized as drivers of recent adaptation underlying dramatic phenotypic change within species [4,5]. **Filamentous pathogens** (i.e., oomycetes and fungi) show an intriguingly tight physical association of TEs with genes encoding virulence factors (i.e., **effectors**) which are essential for host infection [6]. Many of these genes are regulated through the modification of chromatin during infection alongside surrounding TEs [7] (Figure 1A, Key figure). We argue here that the short-term benefits of such TE and effector gene associations have likely trapped plant pathogens in a devil's bargain.

Pathogen effectors are virulence factors – small secreted proteins that manipulate the host physiology and immune system to the advantage of the pathogen [8] (Box 1). Successful infections often depend on finely calibrated effector expression [7]. Effectors are expressed mostly during the early phases of infection and contribute crucially to the suppression of host defenses (Figure 1A). Pathogen genomes typically encode dozens to hundreds of effector genes, mostly in gene-poor regions enriched in repeat sequences. By contrast, housekeeping genes are typically located at a greater distance from repetitive regions [9,10]. The reasons underlying the colocation of effectors and TEs have been widely debated [9,11]. What is known is that effectors are some of the most rapidly evolving genes in genomes [7,12]. In some cases, TEs have been shown to drive rapid sequence evolution of regions encoding effectors or rapidly evolving pathogen minichromosomes [13,14]. The mostly young effector genes may have arisen recently in such repetitive regions, more easily tolerate the insertion of TEs, or have been translocated into such regions. We should also consider that, in some pathogens, effectors are located in highly recombining regions [15–17]. Recombination hotspots frequently evolve rapidly [18]. At present

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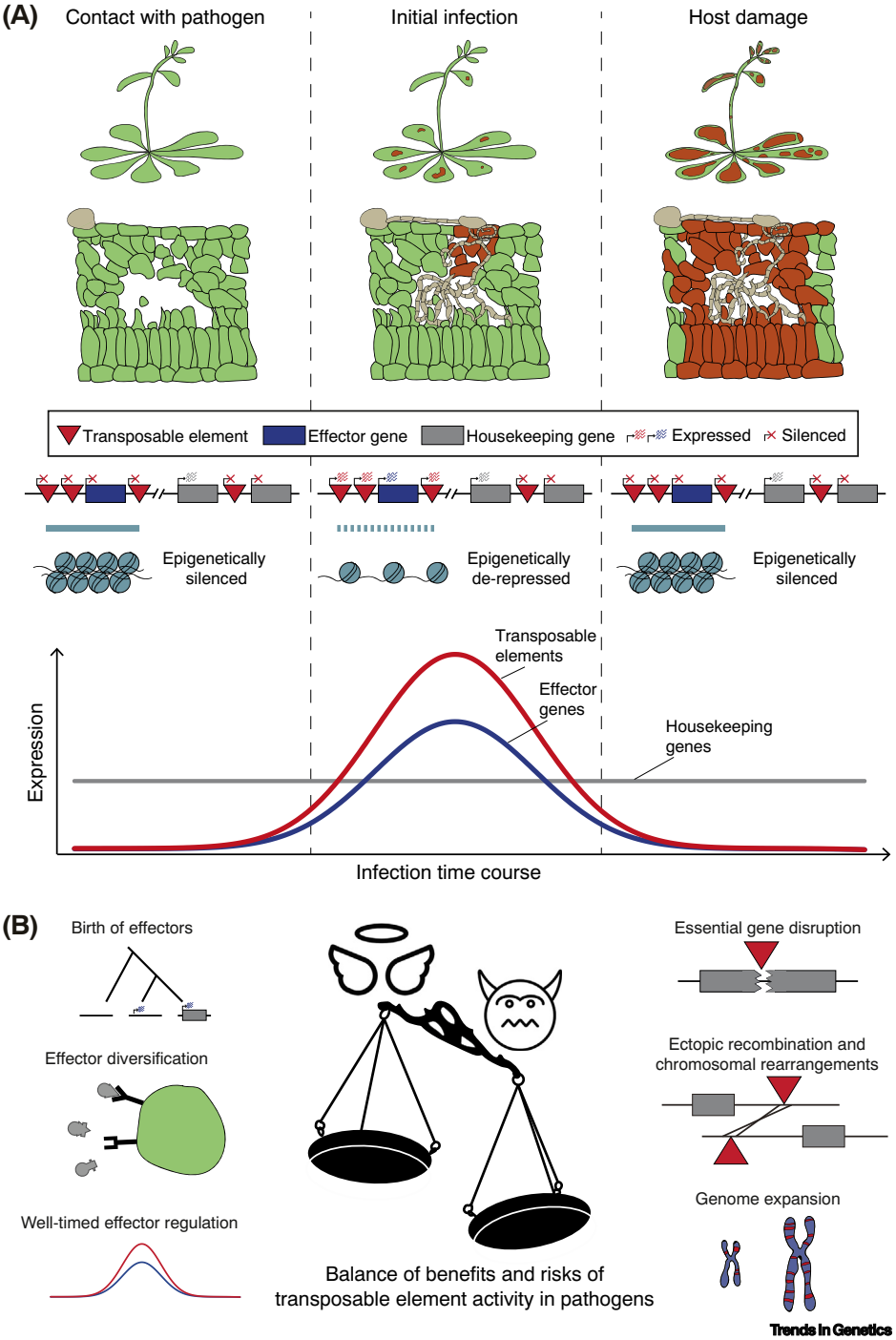
Key figure

The entanglement of virulence factors (i.e., effectors) and transposable elements (TEs) in plant pathogen genomes



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Glossary

Ectopic recombination: recombination between non-homologous sequences in the genome. Most chromosomal rearrangements are caused by ectopic recombination.

Effectors: also known as virulence factors, these are proteins secreted by pathogens that play a role in the host–pathogen interaction, often by interfering with or enabling evasion of the host immune response.

Epigenetic regulation: the control of gene expression by changes in the conformation of DNA. Specific methylation of histones largely controls the compaction or opening of DNA.

Filamentous pathogens: fungi and oomycetes that grow as filaments (i.e., hyphae) and cause disease mostly in plants.

Genome compartmentalization: the alternation of gene-rich and gene-poor regions in the genome. Gene-poor regions are often rich in TEs.

Genome instability: an increase in the frequency of mutations and chromosome rearrangements in the genome.

Miniature inverted-repeat transposable elements (MITEs): non-autonomous TEs that do not encode their own enzymes for transposition and therefore rely on other TEs for their mobilization and propagation.

Repeat-induced point mutation (RIP): a fungus-specific genome defense mechanism that targets TEs and other duplicated sequences. RIP introduces point mutations at an extremely elevated rate compared to genomic background mutations.

Transposable element (TE): a selfish genetic element with the ability to insert into new regions in the genome. Depending on the class, TEs use a cut-and-paste or a copy-and-paste mechanism to propagate in the genome.

Box 1. The role of effectors in plant infections

To successfully infect plants, pathogens must either avoid detection by the host or overcome the host immune responses. Pathogens secrete effector molecules, which manipulate the host cell biology, shield the pathogen from the host, or interfere with the host immune response to enable colonization. Effector genes are tightly regulated during infection and perform highly specific functions at defined timepoints of infection [7]. Many effector genes are under epigenetic regulation [7]. In *Leptosphaeria maculans* the effector genes in TE-rich regions that are upregulated during early infection are repressed by histone H3 lysine 9 trimethylation (H3K9me3) [76]. In *Zymoseptoria tritici* effectors are repressed by H3K27me3 in the absence of the plant [27]. Interestingly, in *Verticillium dahliae*, dynamic genomic regions were linked to heterochromatic marking, but effectors were not significantly more enriched for H3K27me3 than other *in planta* secreted proteins [37]. Effectors that colocate with TEs could have been selected because the adjacent TE environment provides beneficial epigenetic control dynamics during host infection. Furthermore, the tight association between effector genes and TEs helps effector genes to be among the most rapidly evolving genes in pathogen genomes [12].

the relationship between TEs and recombination remains cryptic, although in general there is a negative correlation between TEs and recombination [19]. Therefore, it is possible that effector genes diversify either by locating in genomic environments with high rates of recombination or that have elevated mutation rates due to TEs.

Fungi are excellent models to study TE dynamics because of their compact genomes. This is highlighted by the recent discovery of a massive transposon that shuttles meiotic drive genes around the genome in *Podospora anserina* [20]. New TE insertions in fission yeasts underlie the evolutionary dynamics of tolerance to environmental stressors [21]. TE dynamics can drive the emergence of new effectors, effector diversification, and well-timed **epigenetic regulation** (both expression during infection and silencing in the absence of the host) (Figure 1B). In addition, TEs can move regulatory sequences around the genome and alter the expression of genes, similarly to the ONSEN transposon in *Arabidopsis thaliana* [22]. Effector–TE colocation presents a unique opportunity to study conflict and cooperation between the pathogen control of TE activity and the fine-tuned expression of effectors that are essential for colonizing host plants. The infection phase, before the widespread appearance of disease symptoms, marks the most stressful stage for the pathogen [23,24]. Recognition by the host activates the host immune response, including the deployment of antimicrobial compounds, pH change, and programmed cell death at the infection site [23–25]. To successfully hijack host cells, effector expression is orchestrated by alterations in the chromatin state leading to waves of expression changes [26–28]. In concert with effector expression, TEs are derepressed during the early infection phase [7] (Figure 1A), thus weakening the genome's control of TEs. In other words, TE derepression likely comes at the cost of potentially deleterious mutations or chromosomal rearrangements becoming more frequent [29] (Figure 1B). This entanglement between the timely regulation of effector genes and at least a partial loss of TE repression likely confronts species with an evolutionary conflict. The major risks include genome expansions, possibly threatening the persistence of the pathogen lineage (Figures 1B and 2).

Effector genes located in TE-rich regions with epigenetic regulation are found in a wide range of major crop pathogens including the wheat pathogen *Zymoseptoria tritici* and the oilseed rape pathogen *Leptosphaeria maculans* [7]. In both pathogens, effector expression is thought to be

Figure 1. (A) Plant pathogens penetrate the surface of plant tissues to establish an infection and exploit the host. Effector genes are often epigenetically regulated because of their proximity to TEs. Stress imposed by the plant host leads to epigenetic derepression of regions encoding effectors. TEs become derepressed in synchrony with the upregulation of effector genes. (B) The tight physical association of effector genes and TEs constitutes a risky balance of benefits to the pathogen, including rapid effector diversification to escape recognition by the immune system. However, the derepression of TEs allows their replication. Active TEs can disrupt important genes, trigger chromosomal rearrangements, and ultimately lead to bloated genomes.

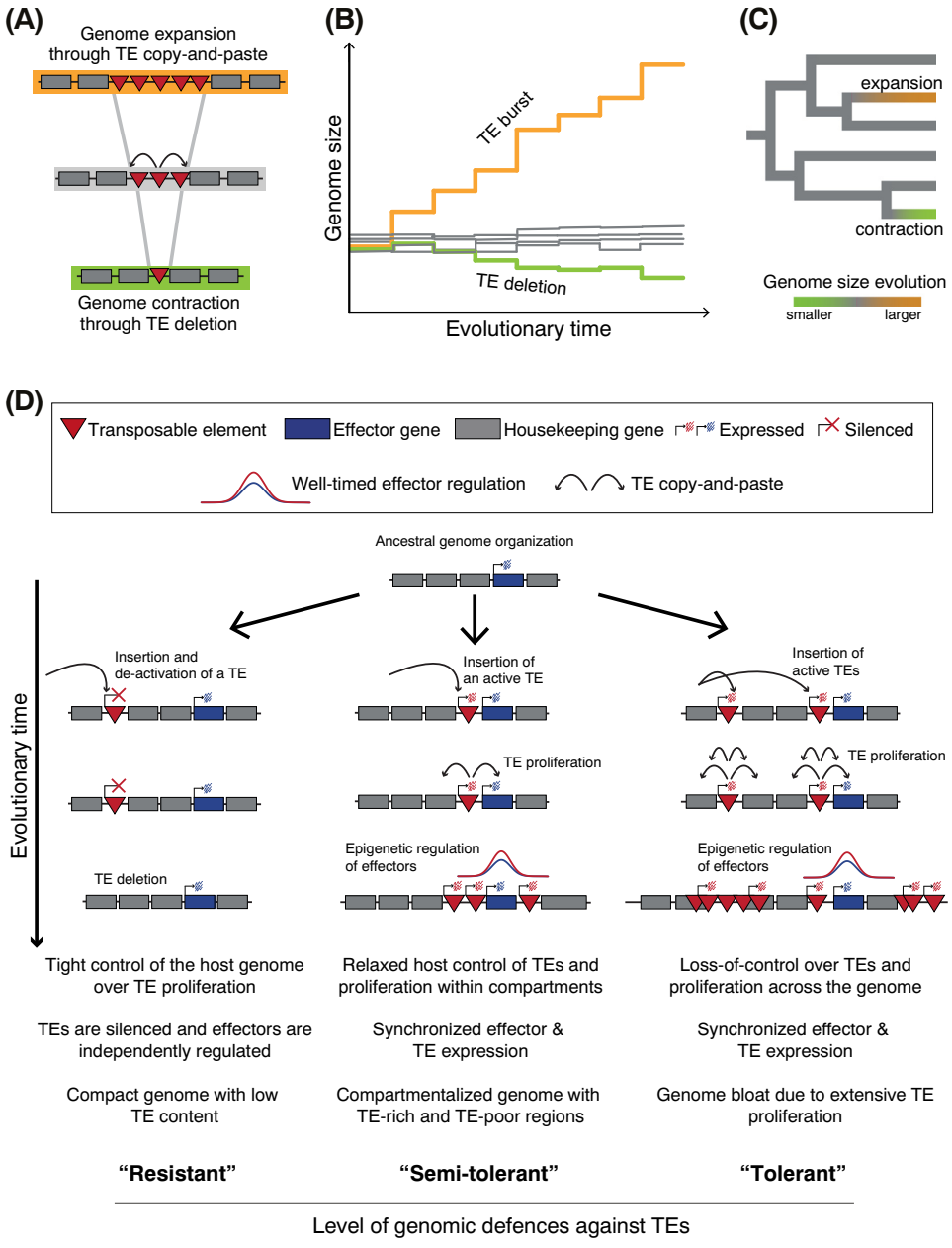

Figure 2. Pathogen genome bloat due to transposable element (TE) activity and genomic defenses. (A) Active copying of TEs can lead to genome size increases. (B,C) Lineages can expand or contract their genomes depending on the activity of TEs. Genome expansions (and contractions) are expected to be restricted to individual lineages. (D) Mechanisms that pathogen genomes use to cope with the activity of TEs. In a hypothetical ancestral genome, no TE is located near to an effector gene. In a genome with highly effective TE defenses, TEs cannot become established and effector gene regulation remains unrelated to epigenetic TE repression. In less-resistant genomes, TEs that insert close to effector genes help to enable epigenetic control of effector genes timed with the onset of infections. TE activity can lead to the creation of TE-rich regions. In 'tolerant' genomes, TE insertions can lead to rapid expansions.

largely governed by changes in the heterochromatin state upon initiation of host infections. Effectors in *L. maculans* are enriched in heterochromatic regions that are mostly repressed in culture (i.e., *in vitro*) conditions but are upregulated during plant infection [28]. Likewise, in *Z. tritici*, the heterochromatic environment of effectors was shown to be a pivotal determinant of their expression [27]. Specifically, heterochromatin is condensed before the pathogen encounters the host, and effector gene expression during infection is mediated by chromatin decondensation in addition to promoter activity. The genome of *Z. tritici* carries a large set of TEs that show rapid derepression upon infection [30]. The broad host range pathogen *Fusarium oxysporum* shows even stronger links between TEs and effectors than most other plant pathogens. Non-autonomous **miniature inverted repeat transposable elements (MITEs)** are frequently found in the promoters of effector genes with a likely impact on expression [31]. There is significant genome size variation between different strains of *F. oxysporum* [32], and the species has a larger genome and a higher TE content than its sister species, *Fusarium verticillioides* and *Fusarium graminearum* [33]. Interestingly DNA transposons comprise 65% of the *F. oxysporum* genome and the most abundant superfamilies are *pogo*, *hAT*-like, and MITEs, of which MITEs are absent in the sister species genome assemblies. Furthermore, in *F. oxysporum*, accessory chromosomes (i.e., chromosomes not shared among all strains) are particularly rich in TEs [33]. Some accessory chromosomes are determinants of pathogenicity and are regulated epigenetically with tight synchronization during host infection [34]. The most comprehensive analyses of epigenetic regulation, TEs, and effectors comes from the vascular wilt pathogen *Verticillium dahliae*. Lineage-specific regions harboring important effector genes are rich in TEs and present specific epigenetic marks that contribute to their evolutionary potential [35–38]. The remarkable co-occurrence of TEs and effectors has broad consequences for pathogen evolution and genome structure.

Risky evolutionary dynamics at effector loci

Derepression of TEs poses a significant risk for pathogen genomes. *De novo* TE insertions can disrupt coding and regulatory sequences in a wide range of organisms [5] (Figure 1B). In humans, several diseases are caused by deleterious TE insertions [39]. Negative effects can also arise from the competition of genes with TEs for transcription factors and from the damage to DNA integrity caused by TE-encoded endonucleases [2]. At the chromosome level, TE proliferation can lead to more repressive histone marks close to new TEs, thus triggering changes in the epigenetic landscape [40]. **Ectopic recombination** between new copies of a TE can cause chromosomal rearrangements [2]. Retrotransposons were recently shown to be the most important drivers of indels, inversions, and duplications in fungal pathogen genomes [41]. However, deleterious insertions are often rapidly removed from the population through purifying selection and are seldom found in coding sequences of eukaryotic genes (e.g., in *Drosophila melanogaster* [42,43] and *Brachypodium distachyon* [44]). A range of fungal species carry a highly sophisticated genome defense mechanism against the proliferation of TEs, called **repeat-induced point mutation (RIP)** [45]. Following the recognition of highly similar sequences in the genome (i.e., a hallmark of active TEs immediately after transposition), the RIP machinery introduces point mutations at a very high rate, leading to non-functional TE copies [46]. RIP mutations also have an inherent bias, and preferentially introduce A/T mutations, leading to a reduced GC content in affected sequences. With the highly effective defenses against TEs come potentially important costs. RIP will mutate any duplicated sequence. Hence, RIP is expected to largely block evolution through gene duplication [45,47]. For pathogens, this likely limits the evolution of effector genes, which are often prone to duplicate owing to the repetitive nature of their chromosomal locations [48].

Recent work on the wheat pathogen *Z. tritici* showed that some of the highly expressed TEs, upon infection, also have among the highest copy numbers in the genome [30]. Hence, the

infection process could well impose a long-term burden on the species by allowing the proliferation of TEs. In the same species, numerous recently inserted TEs are found across the genome [49,50]. Similarly, TE activation upon infection was shown in the human pathogen *Cryptococcus* [51]. Over evolutionary time, bursts of TE activity can drive genome size expansions [52] (Figure 2A–C). Consistent with this, the *Z. tritici* genome shows size variation, and populations with a higher TE content also show more expanded genomes [49,50]. Enlarged genomes and high copy numbers of nearly identical TEs pose serious risks to genome stability by elevating the likelihood of ectopic recombination [2]. The exact triggers underlying genome size expansion are poorly understood. However, the TE expansions observed within species could provide important clues to the process.

Does the plant pathogen lifestyle lead to genome expansions?

Genome size expansions likely driven by TE activity are found in a wide variety of organisms across the tree of life (e.g., [53,54]). However, the evidence for genome expansions is mixed across the phylogeny of fungi and oomycetes. Additional factors to consider are that many fungal pathogens are haploid for the majority of their life cycles and lack a soma/germline distinction. Therefore, all new TE insertions can potentially be transmitted from one generation to the next. Several clades show convincing patterns of genome expansion that coincide with the switch from endophytic to pathogenic lifestyles (Box 2). Examples include the barley pathogen *Blumeria graminis* f. sp. *hordei* (120 Mb and 64% TEs) [55], the poplar rust *Melampsora larici-populina* (101 Mb and 45% TEs) [56], and the wheat stripe rust *Puccinia striiformis* f. sp. *tritici* (83 Mb and 45% TEs) [57]. Similarly, *L. maculans* shows broad epigenetic control of effector genes during infection and has a much larger genome (45 Mb). *L. maculans* also has a higher TE content (32.5% versus <4%) than the closely related species *L. biglobosa* (~31 Mb) [58]. The sister species *L. biglobosa* shows no clear association between effector genes and TEs. *Phytophthora* species are notorious plant pathogens that have significantly expanded genomes (220–280 Mb) [59–61]. Furthermore, in *Phytophthora sojae* at least one effector has been shown to be epigenetically silenced through small RNAs [62]. Genome size expansion in *Phytophthora* pre-dates recent speciation events, and elevated TE activity may therefore have started early in the evolution of the genus [63].

How does TE insertion activity lead to genome expansions? We largely lack evidence that this process plays out in natural populations, but emerging evidence can shed some light on this process [43]. A major factor is likely to be the mode of reproduction. Modeling of TEs in asexual populations predicted TE accumulation and potential population extinctions [64]. In another study, however, no evidence for a higher TE accumulation in natural hybrids of yeast was found [65]. Nevertheless, this could be due to selection because further investigations of laboratory-created hybrids showed that TE accumulation dynamics was genotype-specific [65]. The removal of deleterious TEs can be very efficient [66–68]. In plant pathogens, closely related

Box 2. Genome size expansions in filamentous pathogens

Genome size can differ among closely related fungal species [77,78] and even within a single species [49,50,79]. A striking example of genome size expansion comes from rust fungi that have massively expanded genomes. *Austropuccinia psidii* has the largest assembled fungal genome reported to date (>1Gb with >90% TEs), and the increase in genome size is caused by TE bursts [69]. Expanded genomes are also found in the powdery mildew *Blumeria graminis* f. sp. *hordei* (~120 Mb and 64% TEs) [55] and in the oomycete *Phytophthora infestans* (240 Mb and 74% TEs) [60]. Typically, genome size expansion is driven by derepression of a subset of TEs, resulting in a burst. In *Zymoseptoria tritici*, recent TE expansions were primarily due to *Gypsy* proliferation, whereas population-specific expansions were caused by *Helitron*, LINE, and *Copia* activity [49,50]. A recent lineage-specific genome size expansion in anther smut *Microbotryum* species was driven by *Gypsy*-like TEs [79].

species can display large differences in genome size without any clear association with lifestyle. Interestingly, many pathogens have both asexual and sexual cycles, such as *P. infestans* [60] and *Austropuccinia psidii* [69], making it difficult to disentangle the effects of the reproductive mode. In the near future, analyses of the large genomic datasets available across the fungal kingdom are likely to provide answers to how much genome size evolution is driven by lifestyle.

Is there a resolution to the conflict of TE activity and genome integrity in plant pathogens? The colocation of TEs and effectors is believed to have favored **genome compartmentalization** in some pathogens (Figure 2D). Effector genes are located in TE-rich and rapidly evolving chromosomal regions. Essential genes are shielded from TE-mediated effects in conserved regions of the genome. This compartmentalization has been referred to as the 'two-speed genome' of pathogens [9,10]. Genome compartmentalization may lower exposure to TE activation and help to overcome the negative consequences of the devil's bargain. Some pathogens have retained very compact genomes with a low TE content and no clear association between TEs and effectors (*e.g., F. graminearum* and *F. verticillioides* [33]). Nevertheless, it remains unclear how pathogen genomes have evolved to cope with increased TE activity. Some genomes potentially seem to be 'resistant' to TE activity, largely because of defense mechanisms that prevent proliferation. The mutations introduced by RIP are probably a powerful factor here. For example, *Parastagonospora nodorum* has active RIP [70,71] and a relatively small genome (35–37.7 Mb) with a low TE (<6.2%) content [72,73]. 'Resistance' could also arise from very efficient purifying selection on deleterious TE insertions (Figure 2D). In this case the population size of the pathogen will be a key determinant, and *P. nodorum* shows indeed patterns consistent with such a process [74]. At the other extreme, some filamentous pathogens have bloated genomes with >90% TE content in which essential genes are concentrated in narrow tracts [75]. The large regions devoid of essential gene functions indicate that TEs can insert almost anywhere in the genome without having an impact on fitness. Examples of such bloated genomes include a series of rust fungi and powdery mildews (Box 2), where bloated genomes are hypothesized to have been triggered by loss of RIP and subsequent bursts of TE activity [75]. Such pathogens may be largely 'tolerant' to TE activity because TE proliferation is less likely to have deleterious effects on organismal fitness.

Concluding remarks

Key virulence genes (i.e., effectors) in filamentous pathogens are often located near to TE-rich regions. Pathogens have co-opted the TE derepression dynamics during plant infection to time effector expression. The shared epigenetic landscape of effectors and TEs has obvious benefits for the pathogen. However, derepressing TEs surrounding effector genes has created a risky entanglement that exposes the pathogen to increased TE activity. We propose that pathogens have undertaken a devil's bargain in trading short-term epigenetic regulation of effectors against the long-term risks for the pathogen lineage. The derepression of TEs places a mutational burden on pathogen genomes through increased rates of TE insertions into genes. Ultimately, TE activity in pathogen lineages can lead to genome expansions and higher rates of deleterious rearrangements. TE activities also trigger genomic defense mechanisms, which in turn can have an impact on the expression landscape of the genome. Case studies of crop pathogens highlight that some species may indeed have suffered from recent TE bursts tied to derepression mechanisms. Future research on factors determining the epigenetic landscape of gene and TE expression will elucidate how genomic niches have evolved to benefit pathogens by precisely timing effector regulation (see Outstanding questions). At the same time, the expanding catalogs of fully assembled fungal genomes will help to more clearly establish drivers of genome size evolution. Finally, experimental evolution approaches that manipulate the epigenetic state and TE activity can elucidate emerging mechanisms governing both gene regulation and TE activity.

Outstanding questions

The 'chicken-and-egg' problem – how does the tight association between TEs and effectors evolve? Do TEs preferentially insert near effector genes, or do effector genes translocate into TE-rich regions, comobilize with TEs, or even arise in TE-rich regions? Can we demonstrate the sequence of events of effector and TE colocation in the genome by retracing individual steps in the evolutionary process? What role does chance play in creating such associations?

Escaping the devil's bargain – do some pathogens benefit from joint effector and TE derepression dynamics without suffering from higher TE activity? How do pathogens successfully control TE activity through genomic defenses?

Facing genomic bloat – what are the exact mechanisms of genome size expansion? What roles do pathogen lifestyle, reproductive mode, and genetic diversity play in the onset of genome size expansions? Is the onset of the expansion associated with the emergence of new species?

Do similar devil's bargains exist in other organisms, such as for resistance genes in plants? Is it possible that rapid evolution in pathogens and plant hosts is both facilitated by a dynamic genomic landscape created by the colocation of TEs and effector or resistance genes, respectively.

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Declaration of interests

The authors declare no conflicts of interest.

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