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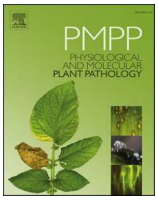

Dynamic Genomes - Mechanisms and consequences of genomic diversity impacting plant-fungal interactions

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A B S T R A C T

The evolution of plant and microbial interactions helps to shape our planet. A major driver of plant and microbial evolution is the selection of beneficial traits borne out of genetic variation. The impact of genetic variation on plant-microbe interactions is well documented, but technological advances have expanded our view of the diversity of genetic variation influencing plant-biotic interactions. The full extent and richness of genomic variation, described here as the dynamic genome, has fueled an amazing array of adaptive traits in plant and microbial populations. In this review, we describe common classes of genetic variation, their mechanisms of generation, examples of their impact on plant-fungal interactions, and technological advancements to define the dynamic genome in plant and fungal systems.

1. Introduction

Dynamic genomes in plant and microbial systems-variation on a theme

The interspecies interactions of plants and microbes sets the stage for one of nature's largest genomic conflicts. Plants in natural and managed systems are inundated with microbes, above and below ground, in need of resources and shelter. Likewise, microbes must compete with one another, survive shifting environmental conditions, and evade the plant immune system in an effort to reproduce. Such large-scale, continual interactions between plants and microbes has resulted in an amazing array of genetic innovations to compete, exploit, cooperate, and survive in nature. As researchers, we often focus on the resulting phenotypic changes caused by genetic variability, but take for granted the origin of underlying genetic mutations. In addition, there has been a bias towards identifying causative mutations that affect short DNA tracts due to technologic limitations. This review article overviews the classes of DNA variants impacting plant and fungal genomes, describes underlying mechanisms that create such variability, and reviews modern approaches for their analysis (Fig. 1a). We pay special attention to dynamic genomes of fungal plant pathogens and their hosts as exemplar systems to observe and understand mechanisms of genomic changes (Fig. 1b).

2. Types of DNA variation present in genomes

2.1. Base substitutions

The most well studied type of DNA variation is that arising from simple base substitutions [1]. This is observed between two individuals that contain a similar segment of DNA in which a single DNA base is changed to any of the other three bases, such as an adenine to thymine (A - > T). Such variation is referred to as a single nucleotide polymorphism (SNP) that is common between related individuals of a species. Single base pair substitutions can arise from various mechanisms. Errors during the replication of DNA can occur, where a non-complementary base is added during synthesis. Replicative DNA polymerases have proofreading activity however, and are generally considered high-fidelity [2]. Single nucleotides can also undergo changes due to chemical modifications and enzymatic activity, such as the variety of mechanisms that have been described to modify cytosines [3]. It has been speculated that cytosine deamination may be involved in repeat-induced point mutation (RIP), a genome defense mechanism in fungi that causes C:G to T:A changes in duplicated sequence [4]. Also, oxidation can affect the chemical structure of nucleotides. For example, as one of the most common forms of oxidative DNA damage, increased content of 8-Hydroxyguanine (8-OHG) has been found in the plant chloroplast DNA upon treatment with ozone [5–7]. Unless repaired before DNA replication, 8-OHG can be mis-repaired with adenine and lead to G:C to T:A substitution [5]. The Base Excision Repair (BER), Nucleotide Excision Repair (NER), and Mismatch Repair (MMR) pathways work together to detect and repair various types of DNA damage, including oxidative damage caused by biotic or abiotic stress and replication errors, ensuring the integrity of the genome [8–11]. The combined action of proofreading polymerases and DNA repair pathways reduce single base changes, but they are still estimated to occur at rates of approximately 1×10^{-10} to 1×10^{-8} per base pair per generation in

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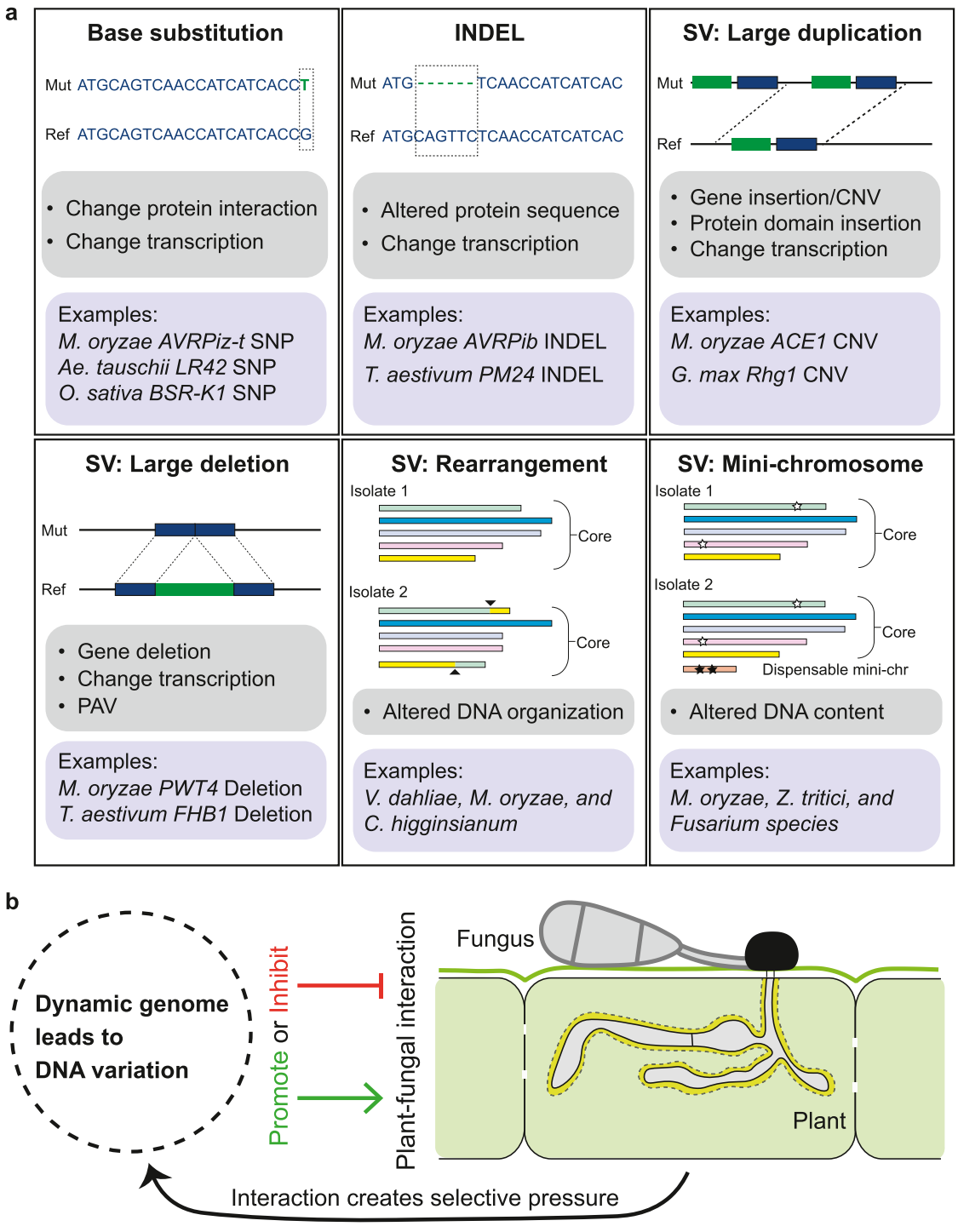

Fig. 1. Types of DNA variation driving dynamic genomes.
(a) Multiple classes of DNA variation can alter DNA function and change plant-microbe interactions. Each box represents a type of DNA variation, listed at the top of each box, as discussed in the text. Example sequences are shown for a mutant (Mut) and reference (Ref) sequence for each DNA variant class. Potential outcomes of the mutation are listed in the grey ovals, and specific examples of genes and organisms effected by the mutation are listed in the purple ovals. Base substitutions change a single base pair, referred to as a single nucleotide polymorphism (SNP) between individuals. Short insertions and deletions (INDEL) are generally considered to affect less than 30 to 50 bps and change downstream transcription and translation. Structural variation (SV) encompasses a wide spectrum of genomic alterations with distinct features and implications. Large duplications of sequences can increase the amount of a transcript and protein or create new protein sequences. Large deletions of sequence may remove a gene or regulatory element. An SV can also more broadly physically change a genome, such as Rearrangements that altering the linear sequence of a chromosome, denoted by black arrows that swap chromosomes ends, shown as different colors. An extreme example of SV can be found in fungi, such as mini-chromosomes that can duplicate sequences and facilitate DNA movement. The figure highlights the impact on coding sequences, such as effectors, that are represent on core chromosomes (white stars) in isolate 1, and duplicated in isolate 2 (black stars). Such duplications can impact the evolution of the coding sequence and host interactions. (b) Genomes are highly dynamic, and a variety of factors can lead to the creation of DNA changes as described in (a). Such DNA variation can sometimes change plant-fungal interactions, such as promoting or inhibiting their symbiosis. DNA variation that leads to an altered interactions is subject to natural selection and can lead to genome evolution in either host or pathogen.

various model (e.g. yeast) and pathogenic fungi (e.g. *Candida albicans*) [12,13]. An exceptional case, with a rate of $\sim 3 \times 10^{-6}$ per base pair per generation has been observed in the model filamentous fungus *Neurospora crassa* [14]. These results likely reflect variation in genome composition and diversity in DNA repair and modification pathways. How such variation impacts an individual species adaptive potential remains largely unknown in plant and fungal systems.

Base substitution can directly impact fungal-plant interactions (Fig. 1) [15]. A ubiquitous example is that between host proteins that directly interact with pathogen effectors. Pathogen effectors are generally defined as proteins or small molecules produced by the pathogen that are secreted into host cells and have a biochemical function to facilitate host infection [16]. The plant immune system is made up of an interconnected network of molecular and cellular components that work together to detect and respond to pathogen challenges [17–19]. The plant immune system is defined as innate, which means that the gene coding sequences are inherited germlinally and do not adapt during the growth of the plant. The immune system utilizes two major classes of immune receptors to initiate defense. One set resides at the cell surface, including receptor-like kinases and receptor-like proteins, while the other set resides in the cytosol, composed of nucleotide-binding leucine-rich repeat (NLR) proteins. Mechanisms of resistance, and cellular outputs can vary between the receptor classes, but it is clear that the different receptors and responses make up a complex and integrated immune response [20].

Following conventional plant pathology terminology, a gene encoding a secreted protein, presumably an effector, that is recognized by a plant host protein, rendering the pathogen unable to cause disease, is termed an avirulence gene [21]. In this case, DNA variation in the avirulence gene that avoids host detection can be beneficial to the pathogen. As such, interactions between plant immune receptors and pathogen proteins are dynamic, and single base substitutions such as SNPs can alter plant-fungal interactions. For example, a single base substitution in the coding sequences of *Magnaporthe oryzae* avirulence gene *AVRPiz-t* can alter the interaction between *AVRPiz-t* and its corresponding resistance gene *Piz-t*, allowing the fungus to overcome host resistance [22]. The same is true for plant receptors, such as the example of an ethyl methane sulfonate (EMS) induced SNP within the LRR region of the wheat leaf rust resistant gene *Lr42* from *Aegilops tauschii* that compromises resistance against *Puccinia triticina* Erikss [23]. In addition to base level substitutions impacting receptor-ligand interactions, SNPs in other coding sequences can affect plant-fungal interactions. For example, an EMS induced SNP in the *Broad-Spectrum Resistance Kitaake-1* (*BSR-K1*) gene, which encodes a rice tetratricopeptide repeats containing protein, confers broad-spectrum resistance against rice blast and bacterial blight diseases [24]. The impact of SNP level variation affecting host-microbe interactions is not unique to plant pathology, such as a recent study involving clinical isolates of the human pathogenic fungus *Cryptococcus neoformans* found that SNPs affecting the RNA interference pathway cause hypermutation and the development of antifungal resistance [25]. Single base DNA variation affecting non-coding DNA can also be important, such as the naturally occurring SNP found in the rice promoter region of the *BSR-D1* transcription factor. This SNP inhibits the expression of *Broad-Spectrum Resistance Digu 1* (*BSR-D1*) and its downstream peroxidases, leading to an increase in hydrogen peroxide levels and an enhancement of resistance against the rice blast fungus [26]. These are only a few examples of the vast literature documenting the impact of SNPs on plant-fungal interactions, but they highlight common examples of simple DNA base level alterations that can profoundly impact plant-fungal interactions.

2.2. Insertions and deletions (INDELs)

Another class of DNA variation commonly observed between related individuals is insertions and deletions, termed INDELs [27]. An INDEL can be identified by comparing two related DNA segments and observing the addition or absence of DNA bases in one of the DNA segments. Generally, INDELs are defined as occurring over short tracks of DNA, classified as short insertion or deletion mutations that change <30 or <50 bp [28,29]. An INDEL may be in coding or non-coding DNA, changing the resulting protein sequence or transcriptional activity. There are different mechanisms that can lead to INDELs, but many of them are related to errors that occur during DNA double-strand break (DSB) repair. DNA DSBs can occur during normal genomic processes, such as replication and cell division, or be caused by exogenous chemical and radiation induced damage [30]. Eukaryotes possess multiple pathways to repair DNA DSBs, some of which can form INDELs [31]. One such highly conserved and active DNA DSB repair pathway is termed canonical non-homologous end-joining (C-NHEJ), which involves end-protection of the DNA DSB ends by the heterodimer Ku70-Ku80, gap filling or excision by a complex of proteins including DNA-dependent protein kinase catalytic subunit (DNA-PKcs), Artemis, DNA polymerase mu and lambda, and restoration of the covalent bonds on the two strands by DNA ligase LIG IV [31–33]. C-NHEJ repair generally changes a few to tens of bases creating INDELs, but there are also examples of perfect C-NHEJ DNA repair that does not cause mutation [34]. Another DNA DSB repair pathway that can result in INDELs does not protect the ends of broken DNA, but instead involves DNA end resection, a processing mechanism in which both 5′ ends of broken DNA are shortened by the action of the Mre11-Rad50-Xrs2 (MRX) or Mre11-Rad50-Nbs1 (MRN) complex in fungi and plant, respectively [31,35]. The two resulting 3′ overhangs at DNA ends are left to search for homologous sequence to anneal, which can occur as minimally as one nucleotide, prior to repair [36,37]. Such short stretches of DNA homology between the two strands can be commonly found between the two strands at a relatively short distance from the initial DNA DSB. An endonuclease complex termed Rad1-Rad10 in budding yeast (also known as Xpf-Ercc1 in plants and animals) can then remove the unpaired 3' flap DNA. Subsequently, DNA polymerase fills in missing bases between the two strands, and the two DNA strands are joined through the action of a DNA ligase, such as DNA ligase III or ligase I depending on the organism [38,39]. In animals and plants, the pathway is termed DNA polymerase theta-mediated end-joining (TMEJ) due to the requirement of DNA polymerase theta (PolQ), while the requirement of a PolQ homolog in fungi is unclear, and we refer to it as microhomology-mediated end-joining (MMEJ) [31]. The TMEJ/MMEJ pathway can result in short INDELs through the action of the nuclease and DNA polymerase during repair [37].

The impacts on plant-fungal interactions caused by INDELs are similar to those described for SNPs, such as altering receptor recognition and virulence, or altering gene expression (Fig. 1). A major difference arising from INDELs versus SNPs, however, is the impact on coding sequence. Given that INDELs impact more base pairs, those occurring in coding sequences could cause a shift in the reading frame, and result in more dramatic mutations, often impacting a protein's domain structure and integrity. Such proteins can have dominant negative phenotypes or be non-functional proteins that are quickly degraded by the cell. For instance, a 6-bp deletion in the *AVRPib* coding sequence in *M. oryzae* allows the fungus to evade recognition by the corresponding rice resistant gene *Pib* [40]. In addition to breaking receptor-ligand interactions, INDELs may also impact host-fungal interactions for recessive traits. A Cas9 multiplex gene editing approach caused INDELs in three wheat *MILDEW-RESISTANCE LOCUS* (*MLO*) homoeoalleles, resulting in resistance against powdery mildew [41]. Additionally, a naturally occurring 6-bp INDEL in the *WHEAT TANDEM KINASE 3* (*WTK3*, also known as *Pm24*) leads to powdery mildew resistance [42].

2.3. Structural variation in the genome

The focus of early genetic and genomic studies, especially where direct genetic attribution was determined for a phenotype, were for SNPs and occasionally INDELs. Analysis on these two types of variants

often ignored larger DNA variants occurring in the genome, broadly defined as Structural Variant(s) (SVs) [29]. More recently, genomic SV is recognized to be a major driver of genomic and phenotypic changes. At a broad level, genomic SVs can be classified as either balanced, in which the genome retains the same total amount of DNA, or unbalanced, in which the amount of DNA is altered [29]. Balanced SV involves DNA translocation or inversion, in which the physical organization of DNA in the genome is altered. Unbalanced SV can result from large deletions, insertions, or duplications of DNA sequences, resulting in altered DNA abundance such as copy number variation (CNV). Additionally, presence and absence variation (PAV) is a type of SV defined by the occurrence of a DNA segment between related genomes. The difference in deletion and insertion events being considered INDELs versus SVs is generally defined based on the length of DNA changed. For DNA variants larger than 30 to 50 bps, the event is typically referred to as an SV [28,43]. The working definition and classification of SVs may continue to evolve as technologic and experimental approaches advance, and we remind readers that edge-cases and grey areas often exist in biology. In the following sections, we provide information on types of SVs, potential mechanisms that create SVs, and their documented impact on plant-fungal interactions.

2.4. Large duplications

Creating an additional copy of a genomic region, referred to as a duplication, can have a significant effect on genome function and organism fitness [44]. Duplications are generally important when they copy coding or regulatory sequence(s) that change a transcript or protein abundance. Duplications can result in sequence copies at the same locus, referred to as tandem duplications, or sequence duplication in trans at physically separated loci, and are generally referred to or identified as CNV [44]. The term CNV is generally not referred to in the context of transposable element sequences, or for whole genome or chromosome duplications affecting ploidy. However, these features and events create sequence homologous DNA sequences that can further create duplications of DNA tracts. This occurs through nonallelic homologous recombination (NAHR), in which repeated sequence similar but nonallelic DNA recombines, leading to duplications and deletions surrounding the event [45]. The length and distribution of repeated DNA greatly influences the frequency of NAHR, although it is likely that additional unknown factors contribute to NAHR regulation [46]. Other mechanisms that can also lead to SV require DNA replication during creation. These include break-induced replication (BIR), fork stalling and template switching (FoSTeS), and microhomology-mediated break-induced replication (MMBIR), reviewed previously [45,47].

Duplications that copy one or more coding sequences can lead to novel functions or impact fitness in two broad ways. One possibility is that the duplicated gene eventually results in an altered protein function, possibly through neo- or sub-functionalization. This was first discovered by the Japanese-American geneticist, Dr. Susumu Ohno, who described how having two copies of a coding sequence could result in relaxed selection pressure for one of them, allowing the sequence to accumulate DNA variation [48,49]. At a presumably low frequency, the duplicated sequence can acquire variation that results in a new protein function, neofunctionalization, or the variant could achieve an independent portion of the original sequence's function, a type of division of labor, termed sub-functionalization [48]. The other way in which duplicated coding sequences can impact fitness, is by affecting the amount of protein present in a cell. Cellular and biochemical processes that are subject to stoichiometric effects or enzyme kinetics can be greatly impacted by DNA duplications. Such sequences can be referred to as having a gene dosage effect, such as duplicating a coding sequence for an enzyme or transporter.

Plant-microbe biology has been substantially influenced by sequence duplication and CNV (Fig. 1). One example is the presence of sequence similar plant immune receptors, sometimes at a single locus, for both extra- and intra-cellular receptors [50,51]. It is thought that strong intergenome pressure imposed by plant-microbe interactions has selected for receptor diversification to recognize new ligands, expanding a plant's immunogenic repertoire [52,53]. Duplicated and diversifying receptors have also likely contributed to the division of labor seen for plant receptors, such as NLR sensor/helper pairs [54,55], and receptor complexes at the cell-surface [56]. Another interesting component of immune perception impacted by duplication is the discovery and description of Integrated Domains (IDs) in NLRs [57]. Described as NLR-IDs (NLR with integrated domains), this subclass of NLRs have been found to carry additional protein domain(s) that are associated with the detection of pathogen effectors [57]. One of the first described examples was the presence of a WRKY domain integrated into the NLR immune receptor RRS1-R (*Resistant to Ralstonia Solanacearum1*) present in *Arabidopsis thaliana* conferring immunity to some plant pathogenic bacterium *R. solanacearum* [58]. In this system, the *R. solanacearum* effector, PopP2, can acetylate the WRKY domain of *A. thaliana* transcription factors to alter their DNA binding and subvert their function to activate plant immune responses. However, the WRKY-ID present in RRS1-R acts as a biochemical trap that can also be acetylated by PopP2, triggering an immune response in junction with the paired NLR RPS4 (*Resistant* to *Pseudomonas Syringae4*) [58,59]. Another well described example of NLR-ID is that of HMA domains present in rice NLRs which activate defense in response to rice blast effectors targeting non-immunity related HMA domain proteins in rice [60,61]. Due to the importance and potential modularity of IDs, several approaches including ID mutagenesis and ID swapping have been developed to engineer NLR-mediated resistance in plants [57]. Related to the dynamic genome, is the question of how NLR-IDs have come to be? The molecular mechanism underlying the insertion of IDs remains poorly understood, but it is presumed that an event related to DNA transposition or ectopic insertion is responsible for duplicating already present domains into NLR coding sequences [62].

Duplications and CNV affecting plant immunity are not confined to canonical receptors. A clear example is the CNV locus in soybean that confers resistance to the major economic pathogen, soybean cyst nematode [63]. The resistance locus, originally termed *Rhg1*, displays substantial CNV across commercially grown varieties [64]. The duplicated region is approximately 31 kb and encodes for multiple open reading frames contributing to the resistance phenotype, which is present up to 10 copies in some resistant varieties [63,64]. Other examples have been identified the association between CNV and plant resistance to multiple diseases including Goss's wilt of maize [65] and potato late blight [66].

Plant pathogenic fungi have also experienced increased fitness through the effects of duplication and CNV. The presence of repetitive sequences in fungal genomes can provide sequence similar templates for the action of repair and recombination-based mechanisms to influence genome variation [67,68]. The clearest examples may be through the expansion of transporter proteins and enzymes capable of conferring fungicide resistance. For instance, the copy number of CCA gene cluster (which includes cyanse and carbonic anhydrase for detoxifying fungicide cyanate) varies among several members of *Fusarium oxysporum* species complex (FOSC) [69]. Interestingly, all the novel CCA gene clusters are located on accessory chromosomes, which might promote the cluster CNV within lineages [69]. More specific for host infection, the expansion of certain effectors and regions coding for secondary metabolites through duplication can increase pathogen virulence. For instance, the CNV in *AVRSr27* locus in *Puccinia graminis* f. sp. *tritici* (Pgt) contributes to the virulence of stem rust in wheat [70]. Recent duplication of an avirulence gene *ACE1* containing secondary metabolites has been observed in a clonal population in *M. oryzae* [71]. CNV also has been found for RXLR effectors in the oomycete *Phytophthora sojae*, while the extent to which they contribute to virulence is not yet clear [72]. Additionally, frequent duplications or losses of genes involved in stress adaptation occur in fungi [73,74], which indicates the significant impact of CNV on fungal evolution and adaptation. Therefore, we speculate that

CNV of effector genes is currently underappreciated as a general mechanism regulating virulence and adaptation that deserves further exploration.

2.5. Large deletions

In addition to duplicating large tracts of DNA, deletion of DNA can occur through varied mechanisms resulting in phenotypic effects. Large deletions are classified as SVs and not INDELs based on their size, with SV deletions spanning thousands to millions of absent nucleotides. When deletion variants are considered on a population scale, researchers may count and classify regions for PAV. One mechanism that can lead to larger scale deletions and PAV is a type of DNA DSB repair termed single-strand annealing (SSA). This DSB repair pathway requires end resection, similar to the TMEJ/MMEJ pathway, but 5′- 3′ end resection during SSA is thought to employ an additional nucleolytic complex (i.e., Exo1 or Sgs1-Dna2) that results in longer DNA end resection [27]. By the very nature of employing longer end resection, the amount of DNA removed from the genome during repair results in longer deletion events. Another difference is that DNA DSB repair through SSA usually involves longer tracts of homologous DNA (typically >25 bp) at the site of repair [31]. Recently, we discovered up to 56 kb large DNA deletions triggered by Cas12a editing from different loci in *M. oryzae*. Intriguingly, these large deletions are resolved between repetitive DNAs, implicating repair by the DNA DSB pathway SSA [75], but other mechanisms may be responsible.

Numerous examples of effector PAV in pathogen populations suggest that large deletions are an important driver of genome variation during host-pathogen interactions (Fig. 1) [76]. Large deletions can remove whole coding sequences, which could result in avoiding receptor recognition, similar to the actions described for INDELs [40]. Evolutionarily, the beneficial effects of such deletions overcoming recognition are countered by possible detrimental effects of losing the biochemical or functional output the effector was supplying for host infection or survival. An interesting aspect of plant-fungal interactions related to large deletions and microbial perception is that of host-range. When a recognized effector (i.e., avirulence gene) is lost, a microbe cannot immediately become a symbiont on that host, as other receptors or immune outputs may prevent host colonization. However, breaking down specific effector recognition can allow non-adapted pathogens a window onto a new host. While the non-adapted pathogen may only marginally colonize and reproduce in this scenario, prolonged interaction may allow the accumulation of additional genetic changes, which are not well understood, resulting in increased host adaptation. This is a proposed mechanism to help explain the emergence of the wheat blast disease caused by *M. oryzae* isolates that are able to infect wheat, *Triticum avenue*. Evidence suggests that *M. oryzae* isolates that were adapted to perennial rye grass (*Lolium perenne*) termed *M. oryzae lolium* (MoL) were in part able to make the host jump to wheat because of the loss of two *AVR* coding sequences (i.e., *PWT3* and *PWT4*) and the deployment of the susceptible cultivars (i.e., *rwt3* wheat) [77]. Similarly, it has been hypothesized that the frequent deletion of putative effectors plays a role in the host jump from monocots to dicots in the smut fungus *Melanopsichium pennsylvanicum* [78]. In addition to host-range and adaptation, large deletion can also create novel resistance in plants. For instance, a 752-bp deletion in a coding sequence for a histidine-rich calcium--binding protein was identified to confer *Fhb1* resistance, a widely used resistance gene in wheat against Fusarium head blight, a devastating fungal disease [79].

2.6. Large-scale rearrangements-translocations and inversions

Another aspect of genome dynamics is the physical arrangement and structure of chromosomes. These types of variation can be more difficult to detect experimentally, as they are often overlooked in routine short-read sequencing projects. More specific and complicated techniques, described in more detail in a subsequent section, are needed to capture changes in physical chromosome structure. Translocation is the exchange of DNA segments between two independent chromosomes, while an inversion is the reversing of DNA sequence between two boundaries on a single chromosome. Following a translocation, the overall sequence content of the genome may remain largely unchanged, but the physical re-arrangement of DNA on chromosomes may result in further genetic or genomic instability, leading to further genomic change. For inversions, nucleotides at the junction may form new sequences, creating new gene products or juxtapose new regulatory sequences. Large rearrangements may have broader effects on the epigenome, chromatin arrangement, or nuclear positioning, further impacting genome function. Such changes could have broader impacts on transcription and DNA stability, and thereby influence a broader segment of the genome beyond the DNA segment originally involved. It is frequently, but not always, observed that intra- and inter-chromosomal translocations in human genomes involve some length of homologous DNA at or around the chromosomal breakpoint [80]. Detailed analysis of chromosomal breakpoints in the soil-borne fungal pathogen *Verticillium dahliae*, identified that repetitive sequences in the form of transposable element (TE) DNA were frequently found at breakpoints [81]. This may indicate the action of NAHR, but experimental evidence is not available. Similar descriptions of TE mediated or implicated genome rearrangements were also reported in other pathogenic fungi, including *M. oryzae*, *Colletotrichum higginsianum* and *Zymoseptoria tritici* (Fig. 1) [82–84]. A recent report also discovered the similar TE-mediated deletion for the avirulence gene *AVR-Mgk1* that located on a mini-chromosome of *M. oryzae* [85], discussed more below.

2.7. Dispensable mini-chromosomes

The previous sections described types of genome variation that involved the addition, deletion or rearrangement of nucleotides on mainly core chromosomes of plants and fungi. Another type of genome variation contributing to dynamic plant and fungal genomes is that of dispensable, accessory, and mini-chromosomes. We are treating these terms, along with supernumerary chromosome, extra-chromosome, B-chromosome in a similar fashion, and our unifying description is DNA segments, self-capable of segregation during cell division, are not required for organism growth and reproduction, and they display variable presence across individuals of a species. Specific mechanisms regarding supernumerary chromosome genesis, maintenance, and inheritance remain to be determined, but it is clear they are commonly present in a number of plant pathogenic fungi, and in some cases, have a substantial impact on plant-fungal interactions (Fig. 1) [86]. It has been shown that the dispensable chromosome is necessary for pathogenicity toward different plant hosts within *Fusarium* species [86]. While loss of the dispensable chromosome can alter the virulence of wheat pathogen *Z. tritici* in a host-species dependent manner [87]. In *M. oryzae*, supernumerary chromosomes consist of a few megabases of DNA sequences, which are typically smaller than core chromosomes and therefore frequently referred to as mini-chromosomes [88]. Compared to indispensable core chromosomes, supernumerary mini-chromosomes in *M. oryzae* are more repetitive with lower gene density. The transposon-rich mini-chromosome provides abundant homology for genomic rearrangements, which may accelerate genome evolution [89,90]. In addition, the crosstalk was indicated between mini-chromosomes and ends of core chromosomes containing many effector genes [89,91]. The mini-chromosome is therefore speculated to play a mediator role for the mobility of effector genes among core chromosomes. It has been proposed that the increased aggressiveness of wheat blast disease may be connected to the presence of mini-chromosomes in the blast fungus *M. oryzae*, and efforts to study the underlying mechanism are ongoing [89,90,92].

2.8. Approaches to capture and analyze dynamic genomes in plant and fungal systems

The advancement of various sequencing platforms (e.g., Illumina, PacBio and Oxford Nanopore) has significantly facilitated the acquisition of high-quality genomes at reduced costs. Since the release of the *A. thaliana* genome in 2000 and *M. oryzae* in 2005 [93,94], numerous genomes of plant and phytopathogenic fungi have been investigated. This has led to a significant acceleration in the study of genome variation and diversity in plant and fungal systems at a population level, especially using detected SNPs [95,96]. However, the detection of SV between genomes remains challenging, primarily due to the complexity, heterogeneity, and size of SVs [29]. An original approach to assess genomic diversity used Contour-clamped Homogeneous Electric Field (CHEF) electrophoresis developed to separate large chromosomes, leading to the discovery of karyotype variation and mini-chromosome in *M. oryzae* and other organisms [88]. Later, the Bionano Saphyr® system uses optical genome mapping to detect SV by imaging intact DNA molecules cut with known restriction enzymes [97]. In addition, cytogenetic techniques such as Fluorescence In Situ Hybridization (FISH) and array Comparative Genomic Hybridization (aCGH) are long-standing techniques to observe genome variation, but the techniques are highly-specialized and laborious [63,98]. To overcome these difficulties, new techniques are being developed to further track specific types of genetic variation at the level of individual loci. Amplicon sequencing, which uses PCR enrichment followed by Illumina sequencing, is commonly used to dissect the genetic variation within populations [99]. The use of high-throughput conformation capture (Hi-C) can provide a solution for studying large-scale SV [100]. Long-read sequencing can now capture large SVs, such as dissecting a ~56 kb deletion caused by Cas12a editing in *M. oryzae* [75]. Additional efforts have sought to enrich specific DNA regions prior to long-read sequencing. For example, nanopore long-read sequencing has been combined with targeted CRISPR-Cas9 DNA digestion in a technique termed nCATS to selectively sequence CRISPR digested regions [101]. The approach allows PCR amplification free, long-read sequencing of genomic regions to enable the detection of SNPs, SVs and DNA methylation profiles [101]. A similar strategy, termed Cas9-assisted targeting of chromosome segments (CATCH), used Cas9 digestion, size selection, and nanopore sequencing to implement large-scale targeted sequencing of large genomic regions [102]. In addition, a novel target-enriched sequencing method called Xdrop, utilizes a microfluidic system to sort DNA regions of interest based on complementary target pairing, applied to resolve large and complex DNA rearrangements caused by genome editing [103,104]. Moreover, Single-cell sequencing is also a promising method for resolving genome heterogeneity within populations of cells [105].

2.9. Computational advances

Significant effort has gone into identifying SVs from high-throughput sequencing data. Both short and long sequencing reads were widely used for identification of SV based on read alignments to a reference genome. Read depth approaches use read depth to quantify the copy number of DNA sequences, such as CNVnator [106] and CGRD [89,107]. CNVnator infers CNV based on read alignments from a single genome. The CGRD approach uses read depth to compare two genomes, which can identify CNV regions in the kilobase scale. The read depth approach is sensitive to the sequencing bias due to extreme GC content and the alignment bias due to genomic repetitiveness. The method such as CNVnator reduces the impact of such biases through modeling for bias correction. The CGRD method accounts for such biases by recommending comparison of similar sequencing data that share biases. CGRD is effective at detecting large PAV between two genomes. Split alignments of reads to a reference genome and unexpected alignment coordinates of paired reads can be used to infer SV, which are implemented in the algorithms such as Breakdance [108], DELLY [109], and LUMPY [110]. Although dedicated computational algorithms have been developed for inference using short reads, the ability of SV detection is limited by the length of short reads. Long reads help span large SV and reduce the portion of inaccessible genomic regions due to high repetitiveness [111]. Multiple methods, such as PBHoney [112], Sniffles [113], SVIM [114], NanoVar [115], and SVision [116] have been developed for SV discovery using long reads.

Complete or nearly complete genome assemblies can greatly facilitate the identification and analysis of genomic variation [117], and while they are challenging to generate, highly contiguous assemblies are available for even the most challenging species [118,119]. When telomere-to-telomere (T2T) assemblies can be produced, a sophisticated whole genome aligner such as Nucmer [120] is needed to handle alignment gaps and repetitive sequences. We note, when interpreting genome comparison results between highly assembled genomes, the impact of potential assembly errors still needs to be considered. By combining Nucmer with Syri, a pipeline to identify synteny and SV between two genomes [121], SVs such large PAV, duplication, inversion, and translocations can be readily visualized, as demonstrated between *M. oryzae* genomes [92].

3. Conclusion

The feedback between technological, computational, and experimental advances pushing our understanding of the dynamic genome is not slowing down. Exciting advancements in these areas will continue to update our understanding of plant-fungal interactions and evolution. Plant-fungal interactions remains an excellent model to understand and manipulate eukaryotic co-evolution, and understand basic process of genome function. Advancing our basic understanding of molecular mechanisms leading to the generation of genome variation will spur further innovation. The development of more rules-based knowledge on genome function will expand our avenues to develop novel detection, protection, and response strategies. The era of precision agriculture, capitalizing on our knowledge of the dynamic genome to aid genome engineering, synthetic biology, and predictive modeling efforts may arrive in the coming decade.

Declaration of competing interest

SL is the co-founder of Data2Bio, LLC. Other authors claim no competing interest.

Data availability

No data was used for the research described in the article.

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