Evolution of resistance gene specificity

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Abstract

In Plants, resistance genes (*R* genes) are generally a part of large gene families, which are known to show significant variation within and between different plant species. It has been hypothesised that *R* genes have evolved different specificities to recognize a wide range of potentially fast evolving pathogens. In this review we illustrate the main mechanisms that generate *R* gene diversity and provide examples of how they can change *R* gene specificity. Next, we explain which evolutionary mechanisms are in place and how they determine the fate of new *R* gene alleles and *R* genes. Finally, we place this in a larger context by comparing the diversity and evolution of *R* gene specificity on within and between species scales.

Introduction

Plants rely on effective defence mechanisms to mitigate potentially harmful interactions with microbes. Recognition of microbes and down-stream activation of plant immunity is mainly mediated by genes encoding receptor-like proteins (RLPs), receptor-like kinases (RLKs) and nucleotide-binding oligomerisation (NOD)-like receptors (NLRs). These receptors are deployed at various subcellular locations, and differ in their domain structure, their level of recognition specificity and the mechanisms by which they recognize invaders.

Recognition of microbe/pathogen associated molecular patterns (M/PAMPs), such as flagellin or chitin at the plant cell surface, is mediated by RLKs and RLPs known as pattern-recognition receptors (PRRs). PRR signalling outcomes prevent the proliferation of most microbes on plant hosts. This kind of resistance is considered to be polygenic, as the (inter)action of several PRRs defines the resistance

phenotype. Adapted pathogens secrete variable molecules, named virulence factors or effectors, into their host to promote infection, e.g., by interfering with PRR down-stream signalling. Resistance based on recognition of these specialised effectors is mediated by single dominant genes that are historically termed Resistance (*R*) genes. *R* genes predominantly encode NLRs (Dodds and Rathjen 2010). The canonical protein domain structures of NLRs consists of a variable N terminal domain, a central nuclear binding site, and C-terminal leucine rich repeat (LRR) domains (Shao et al. 2016). Some apoplastic effectors are recognized by *R* genes encoding surface localised transmembrane receptor-like proteins (RLPs) with extracellularly localised LRRs (Thomma, Nürnberger, and Joosten 2011).

NLRs and RLPs either directly bind effectors (direct recognition) or detect effector-mediated changes to the host's physiology (indirect recognition) for activation of downstream signalling (Cesari 2018; Kourelis and van der Hoorn 2018). In some cases, domains that resemble effector host targets are integrated into NLR structures, where they mediate direct interaction of the effector with the *R* gene (integrated decoy recognition) (Cesari 2018). The exact mechanisms downstream of RLP and NLR activation that trigger resistance responses are just being unravelled and are reviewed elsewhere (Pruitt et al. 2021; I. M. L. Saur, Panstruga, and Schulze-Lefert 2021).

Specificity of an *R* gene or single variants of an *R* gene (alleles) can be molecularly defined as the range of effectors that the resulting *R* gene product detects during resistance signalling activation. Previous studies have shown that NLR specificity is often mediated by the Leucine-rich repeat domain (Qiu et al. 2007; Krasileva, Dahlbeck, and Staskawicz 2010; Bauer et al. 2021). Yet, the TIR-domain has also been implicated in specificity (Nishimura et al. 2017) as well as integrated domains (IDs) (Białas et al. 2021). Both NLRs and RLPs often occur in large gene families (Jupe et al. 2012; Luo et al. 2012; Lin et al. 2013; Jia et al. 2015; Van de Weyer et al. 2019), ranging from close to 200 NLRs in the model plant *Arabidopsis thaliana* up to 1000 NLRs in apple (*Malus domestica*). Here we take a closer look into the evolution of *R* gene specificity. Therefore, we introduce the major forces driving the evolution of *R* gene specificity: mutation, insertion or deletion and recombination (Figure 1), followed by the forces that shape, maintain and expand *R* gene diversity over time in plant populations (Figure 2). We illustrate each of these processes with examples.

Evolutionary mechanisms generating new* R *gene specificities

As for any gene, genetic diversity of *R* genes is generated by mutations, insertions and deletions and recombination (Figure 1).

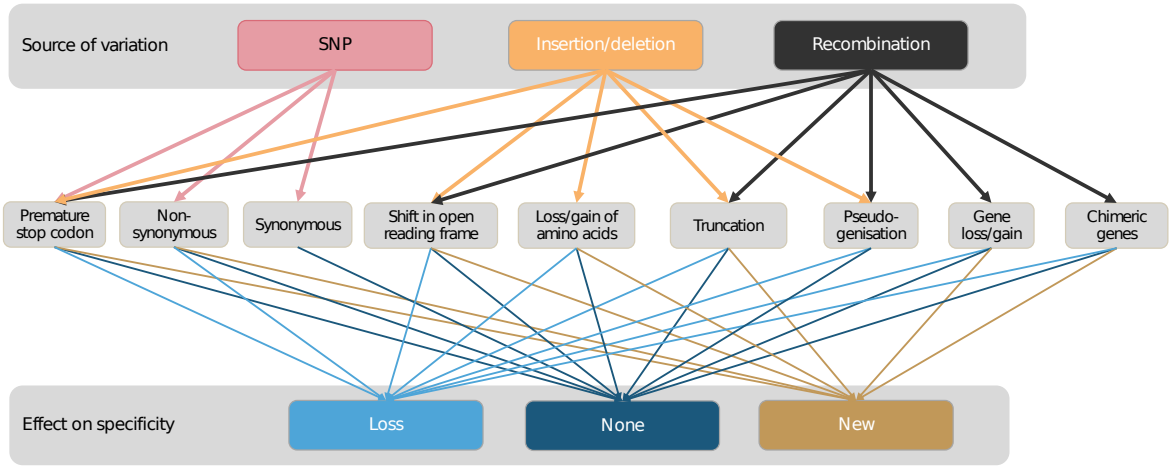

Figure 1 Diversity in R genes can generally be generated by one of three processes: mutations (SNPs), insertion/deletion of larger of smaller gene fragments and recombination. The potential effects of these events can differ on the nucleotide and amino acid level. Each of these events can potentially alter the specificity of R genes (loss of specificity or gain of specificity) or have no effect.

Single nucleotide polymorphisms (SNPs) and insertions or deletions of several base pairs are thought to be major drivers of changes in *R* gene specificity. Examples include the NLR *R3a*, which recognizes the *Phytophthora infestans* effector Avr3a. Two non-synonymous SNPs, resulting in the *Avr3a*^{EM} allele, render *R3a* unable to recognize this variant (Armstrong et al. 2005). In turn, single SNPs in one of the *R3a* LRR-coding regions result in *Avr3*^{EM} recognition. Eight SNPs, located across the *R3a* gene, expand its specificity and allow it to also recognize an Avr3a variant from the related species *P. capsici* (Segretin et al. 2014). SNPs also affect the specificity of many other NLRs and RLPs, including, but not limited to, the *I2* gene, which mediates *Fusarium* resistance in tomato (Giannakopoulou et al. 2015) and *Pm5e*, a powdery mildew resistance gene in wheat (Xie et al. 2020).

Recombination has long been hypothesised to be a major driver of *R* gene diversification. The frequent organisation of *R* genes in clusters (Andolfo et al. 2013; Bai et al. 2002; Fritz-Laylin et al. 2005; Guo et al. 2011; Jupe et al. 2012) along with their leucine-rich repeat domain, makes them prone to inter-allelic cross-over, unequal crossing-over ectopic recombination, and gene duplication (for reviews see i.e., Michelmore and Meyers 1998; Leister 2004). Adapting a concept for the evolution of the human major histocompatibility complex (MHC), Michelmore and Meyers (Michelmore and Meyers 1998) proposed the birth and death model for the evolution of *R* genes. Their model suggests a major role of inter-allelic recombination for the diversification of specificity. Unequal crossing-over within gene clusters can generate new resistance genes that can increase in frequency in the population if advantageous (Michelmore and Meyers 1998).

Early studies on *R* genes already revealed the important role of recombination. One of the first cloned *R* genes was *Cf-9*, from tomato (*Solanum lycopersicum*), which encodes an RLP recognizing *Cladosporium fulvum* effector Avr9 (Jones et al. 1994). *Cf-9* resides in a locus with five homologs, dubbed A-E, with *Cf-9C* actually recognising Avr9 (Parniske et al. 1997). In the wild tomato species *S. pimpinellifolium*, recombinant versions between two of these alleles can be found, dubbed *Cf-9DC*. All recognize Avr9 (Van der Hoorn et al. 2001). RLP recombination also happens in monocots. The wheat *TaRLP1*, which confers resistance to *Puccinia striiformis f. sp. tritici*, resides in a cluster and the functional allele $TaRLP1_{800}^{-2}$ seems to be a recombinant between two other allelic variants in the cluster (Jiang et al. 2013).

The resistance genes *Lr1* and *Lr21* provide evidence that recombination events shape both NLR evolution and *R* gene specificity. The genes (originally derived from *Aegilops tauschii*, a diploid wild relative of wheat) encode NLRs with resistance specificity to the leaf rust fungus *Puccinia triticina* in bread wheat. The functional *Lr* alleles that have been bred into wheat are the result of a foregone recombination event between two non-functional *Lr* haplotypes in the diploid wild wheat relative (Huang et al. 2009; Krattinger and Keller 2016; Marcussen et al. 2014; Qiu et al. 2007). For *Lr1*, the region could be mapped to the segment encoding the LRR region of the NLR gene, indicating that this region defines the specificity of *Lr1*.

Evolutionary mechanisms shaping the fate of *R* gene specificities

Knowing that SNPs and recombination events can rapidly generate genetic variation which potentially alters specificity, this section will examine the evolutionary mechanisms that determine the faith of new variants in a plant population.

The fate of an allele in a population (loss, maintenance, or fixation) depends on the dynamic interplay between genetic drift, the strength of selection, and the fitness effect of the variant in the given environment and genomic context (Figure 2). I.e., plants interact with dynamic pathogen communities with different effector repertoires. Genetic drift describes random changes in allele frequency due to random survival of offspring. The strength of selection depends on the effect (neutral, positive, negative) of the mutation on host fitness. New *R-gene* alleles (new specificity or loss-of-function alleles) and newly generated *R*-genes, i.e., resulting from a tandem duplication, can become fixed in a population by directional selection if they have a fitness advantage compared to existing variants, i.e., they have a beneficial new effector recognition specificity. Conversely, several alleles of a single *R* gene can be maintained as a balanced polymorphism because of heterozygote advantage (positive correlation between heterozygosity and fitness fitness'), negative frequency-dependent selection (inverse

relationship between fitness and allele frequency), spatially or temporally varying selection and context dependent fitness costs (i.e., cost of resistance in the absence of effectors) (Brown and Tellier 2011).

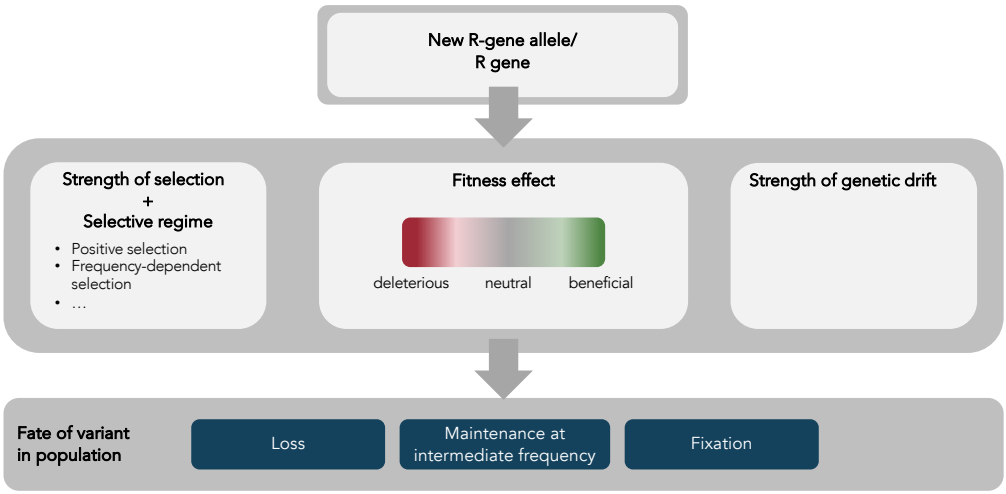

Figure 2 Once variation has been introduced, the interaction of three main factors determines the fate of the variant. The strength of selection (and type of selection) itself, the fitness effect of the variant in the given biotic interactions (pathogen communities, pathogen abundances) and genomic context (i.e., epistatic effects, functional costs) and the amount of genetic drift in the population. As a result of this dynamic interplay new R gene variants (including new specificities) can be fixed, maintained at intermediate frequencies, or be lost in the population.

Interactions between *R* gene and effectors can give rise to co-evolutionary dynamics. These dynamics span a continuum from arms-race dynamics (Dawkins and Krebs 1979) where novel *R* gene alleles become fixed but are quickly overcome by counter-adaptations in the pathogen to trench-warfare dynamics (Stahl et al. 1999) where several alleles (resistance/susceptibility, different specificities) are maintained for extended periods of time. Analyses of genomic data have revealed diverse evolutionary histories of individual NLRs ranging from selective sweeps to long-term balancing selection (Bakker et al. 2006; Rose et al. 2004; Stam, Scheikl, and Tellier 2016).

Besides selection, genetic drift can play a role in shaping the evolutionary history of *R* genes: especially in small populations. Genetic drift random changes in allele frequencies due to random sampling of offspring from the parental generation. If population sizes are small, genetic drift can even cause the random loss of beneficial variants, which are initially rare, or the fixation of slightly deleterious variants. One example illustrating the potential effect of drift are the southernmost populations of the wild tomato species *S. chilense*. These populations have completely lost *Cf*-mediated resistance (Kahlon et al. 2020) and are characterised by a comparatively small estimated effective population size, as well as being the most distant from the centre of origin (Stam, Silva□Arias, and Tellier 2019).

_R_ gene repertoires within species, differences between populations

It is widely hypothesised that *R* genes are under strong selective pressure to constantly keep pace with diversifying pathogen effectors. Therefore, it is expected that *R genes* potentially harbour more variation (i.e., non-synonymous SNPs in the coding region) than the genome-wide average of genes.

Work on *Arabidopsis thaliana* revealed exceptionally high levels of SNPs in some genes of the *NLR* family in a comparison between 62 accessions (Van de Weyer et al. 2019). Values of nucleotide diversity and Tajima's D, which can be indicative of different types of selection when compared to the genome-wide average, were calculated and varied dramatically between individual NLRs, indicating diverse selective pressures. In most of the identified orthogroups (groups of homologous alleles), signals for positive or balancing selection were detected (Van de Weyer et al. 2019). However, no comparisons with other genes were made. A recent analysis of selective pressures in *A. thaliana* RLPs revealed little differences between RLPs that typically function as *R* genes and those fulfilling other functions (Steidele and Stam 2021).

Population-scale studies in the wild tomato species *S. chilense* also found significant variation in SNP levels and evidence for positive selection of several NLRs. However, the majority of assessed NLRs does not show any significant deviation of SNP levels from the genome-wide average, both within and between populations. Some of the NLRs are possibly even under purifying selection (Stam, Silva□Arias, and Tellier 2019). A population-scale study of NLR diversity in the inbreeding wild tomato species *Solanum pennellii* revealed an even more limited number of NLRs with polymorphisms (Stam, Scheikl, and Tellier 2016). However, both studies could not assess the effect of balancing selection due to their sequencing strategy.

Yet, there are numerous other important studies on individual *R* genes that suggest a role for balancing selection. These include *RPP8* (MacQueen et al. 2019) and *RPP13* (Rose et al. 2004) in *A. thaliana*, *Pto* in *Lycopersicon* species (Rose et al. 2005; Rose, Michelmore, and Langley 2007), *Pm3* in wheat (Bourras et al. 2015) and *Mla* in barley (Seeholzer et al. 2010; Maekawa et al. 2019). Multiple *Mla* (*mildew locus A*) alleles are maintained in wild barley and form two MLA subfamilies. A similar ratio of subfamily members amongst individual wild barley accessions suggests a balancing selection mechanism of the subfamilies in the host populations (Maekawa et al. 2019). The maintenance of multiple subfamily 1 *Mla* alleles in the population was thought to be largely the result of co-evolution with the matching effectors from the powdery mildew fungus *Blumeria graminis* formae specialis *hordei* (*Bgh*). However, the isolated *Bgh* effectors recognised directly by different MLAs are not sequence related (Lu et al. 2016; Saur et al. 2019; Bauer et al. 2021). In addition, it was recently shown that subfamily 1 *Mla* alleles also contribute to isolate-specific resistance to the strip rust fungus *Puccinia striiformis* (Bettgenhaeuser et al. 2021). Taken together, these data suggest that the recognition of multiple non-homologous effectors derived from

different isolates, or even unrelated pathogens, contribute to the maintenance of balancing selection at *Mla*.

Diversity generated by recombination can also reveal interesting patterns of selection between populations of a species. *Cf-9* and *9DC* alleles can be found in all *S. pimpinellifolium* populations but the frequency of the *9DC* allele depends on the geographical location and ranges from close to 50% in the southern part of the species' range in Peru, to less than 15% north in Ecuador, indicating spatial variation in selective pressure (Van der Hoorn et al. 2001). In *Solanum chilense,* typical *Cf-9* variants could not be detected, yet up to 65% of the plants can recognise *Avr9*, indicating that indeed recombination can generate alleles that maintain or alter specificity, and selective pressures on such alleles are not uniform throughout species (Kahlon et al. 2020).

One of the most comprehensive studies aiming to understand the maintenance of a balanced presence/absence polymorphism comes from the *A. thaliana* NLR *RPS5* (*Resistance to Pseudomonas syringae* 5)*. RPS5* encodes an NLR that indirectly recognizes several homologs of the *Pseudomonas syringae* effector AvrPphB (Avirulence protein Pseudomonas phaseolicola B) (Warren et al. 1999; Karasov et al. 2014). The close to equal ratio of presence to absence of *RPS5* in a panel of 1,198 accessions from 357 populations and a *RPS5* frequency of 20-80% within single populations confirms that this polymorphism is long-lived and is not linked to population structure or geographic origin. The maintenance of a presence/absence rather than polymorphism over SNP diversity may be explained by a large fitness cost of resistance in the absence of infection (Karasov et al. 2014). The study further revealed that the maintenance of the polymorphism is likely the result of diffuse interactions with several pathogens effectors and species.

Recent pan-genomic studies of NLR diversity have revealed large intraspecific variation in NLR repertoires, likely suggesting extensive intraspecific variation in NLR specificity (Figure 3) (Barragan and Weigel 2021). In a pioneering study, combining resistance-gene enrichment sequencing with PacBio-Sequencing, van der Weyer et al. (2019) showed that the number of NLRs within 62 world-wide *A. thaliana* accessions varied from 167 to 251, which may indicate differential selective pressures on the NLR component in different *A thaliana* populations. They also found evidence for intergenic recombination in 74% of the classified orthogroups, though they did not assess the actual amount of recombination in each of these groups and how these affect the specificity of the NLRs. In *Solanum americanum*, *Rpi-amr1* lies in a complex resistance locus. Recombination of parts of this *NL*R gene happened between accessions and seem to have an effect on the efficacy with which the NLR can bind the recognized effector *Avr-amr1* (Witek et al. 2021). A more detailed study on NLR copy number variation (CNV) between *A. thaliana* accessions shows big differences between clusters of homologous NLR. Some clusters show no CVN at all, whereas others show major radiations and have more than 20 copies in certain accessions (Lee and Chae 2020).

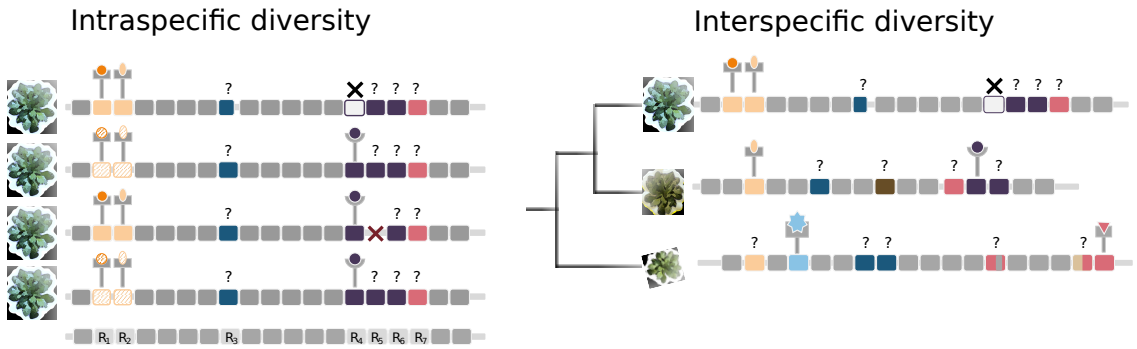

Figure 3 Figure 3 Graphical illustration of possible variation in R genes observed within and between species. A) The variation in R genes that can typically be observed within a species, such as allelic variation (R1 & R3), minor deletions (R3) or presence-absence variation within a gene cluster (R4-R8). B) Over time this can lead to the much larger variation as observed in interspecific comparisons, with multiple presence-absence events, new, unrelated R genes that might have arisen due to recombination with unknown ancestors and R genes with new integrated domains.

Few R genes have receptor – effector interactions drawn on top of them. The question marks above R genes illustrate that, at present, the functions and specificity of most R genes are not known.

Macro-evolutionary patterns of *R* gene specificity

On a macroevolutionary scale, the processes described above can lead to the tremendous interspecific variation in NLR and RLP encoding genes that we see today (Figure 3)(Baggs, Dagdas, and Krasileva 2017; Shao et al. 2014; 2016; Steinbrenner 2020). Unequal crossing over and recombination events predominantly happen within the NLR and RLP gene families. However, in rare cases, such events can also lead to incorporation of TEs, incorporation of genes or genomic regions that are not (yet) functioning as *R* genes, often referred to as integrated domains (IDs) (Baggs, Dagdas, and Krasileva 2017). Such events are often likely detrimental, yet in some cases they can apparently lead to new functionality and specificity of the respective *R* genes. The simplest scenario for gain of specificity is one where the newly integrated domain acts as a decoy for effector targets and that this effector trap activates signalling of the NLR. Some Pfam domains are more commonly found as integrated domains, and these can be plant family or species specific (Sarris et al. 2016). This in turn is in agreement with the hypothesis that the selective maintenance of *ID*-NLR genes is largely based on the virulence targets of the encountered pathogens (Ellis 2016; Kroj et al. 2016). The *A. thaliana* pan-NLRome study also allowed for a comprehensive study of NLR IDs across accessions. *A. thaliana* NLR IDs can be grouped into 36 distinct Pfam domains of which between 5 and 17 could be found within 4–16 *ID*-NLR genes in individual accessions (Van de Weyer et al. 2019). In rice, integrated heavy metal-associated (HMA) domains have been particularly well studied in the last years, as these domains act as direct decoys for a number of effectors from the rice blast fungus *Magnaporthe oryzae* (Cesari et al. 2013; Maqbool et al. 2015; Ortiz et al. 2017). One example is the rice *Pik-1* NLR that recognises the effector *AVR-Pik*. Associations between products of *AVR-Pik* alleles and the polymorphic HMA domains of *Pik-1* correlate with the *Pik* recognition

specificities towards *M. oryzae* isolates, suggesting functional expansion of *Pik-1* in a co-evolutionary process mediated by direct, iterative cycles of NLR and AVR associations (Kanzaki et al. 2012; Maqbool et al. 2015; De la Concepcion et al. 2018). The HMA protein *Pi21* is a blast susceptibility factor, and this is the hypothesised reason for the HMA integration in numerous functional rice NLR genes (Fukuoka et al. 2009).

Although the term 'ID-NLR' became popular in the field only a few years ago (Cesari et al. 2014), the concept has been described earlier. For example, the tomato NLR Prf carries a unique N-terminal domain and in agreement with its function (mediating effector binding *via* the *Pto* kinase) this domain co-evolved with the *Pto* kinase (Mucyn et al. 2006; Grzeskowiak, Stephan, and Rose 2014). Notably, unlike most characterised IDs, this *Prf* N-terminal domain does not cluster into a Pfam domain; potentially because it is not a decoy of the effector target but binds to the effector target *Pto* (Mucyn et al. 2006). In addition, *Prf* carries an additional integrated domain that was previously known as Solanaceae domain (SD). Based on this domain sequence, Seong et al. (Seong et al. 2020) studied 15 wild tomato accessions and found that the domain (now known as *exNT*) is specific to one clade of NLR*s*. It remains to be determined how this domain contributes to the specificity of these NLR genes.

Whenever new species form, no matter the underlying mechanisms, they carry over their parental NLR repertoires. As a result, NLRs that share a common ancestry, which predates the respective species split can be found when analysing the repertoires of different species. Allopolyploidization resulting from hybridization events between two different species can combine NLR repertoires from different species into a single genome (although they may keep evolving independently in the respective subgenomes). This is common in agriculture because new crop species with desirable traits are commonly produced by artificial hybridization.

Conclusions / Outlook

Tremendous progress has been made towards understanding a) the molecular mechanisms underpinning resistance to specific effectors, b) the generation of new specificity by mutation and recombination, c) the amount of intraspecific and interspecific variation in *R gene* repertoires and d) inferring selective pressures from polymorphism data. Yet, there are still gaps to be filled to obtain a more comprehensive understanding on the specific factors governing the evolution of NLR specificity. Comparative genomic studies provide attractive platforms to obtain estimates of allelic and haplotype diversity, to analyse *R*-gene repertoires within local populations and between species, and to infer selective pressures. Yet, without further functional testing of single alleles/genes against a set of effectors or pathogen strains they remain elusive with respect to the specificity range of single alleles/genes and the amount of redundancy in *R*-gene specificity within single accession, populations, and species. More detailed comparative studies that move beyond identification of orthogroups can be challenging. *R* genes often reside in highly dynamic *R*-gene clusters which complicate the assembly of *R* gene loci and can result in confusing

paralogs with orthologs and thus, complicate evolutionary analyses (see also Barragan and Weigel 2021). Several effector-*R* gene pairs that rely on direct effector-receptor associations mediated largely *via* the LRR domain for are molecularly studied (Dodds et al. 2006; Catanzariti et al. 2010; I. M. L. Saur et al. 2019; Krasileva, Dahlbeck, and Staskawicz 2010). Such effector- *R* gene pairs provide attractive platforms to study the evolution of *R* gene specificity and effector genes in populations which are rich in naturally occurring resistance specificities. Yet, molecular and genetic studies of such interaction systems can be experimentally challenging. Genetic complexity of the pathogen and/or the host in combination with either the lack of transformation protocols or extensive times associated with host transformation complicate mapping and validation of the involved *R* genes and effectors.

Studies elucidating the molecular mechanisms of specificity often focus on alleles from a single accession and artificially introduced mutations. While such studies provide elaborate and elegant demonstrations on the mode of action of a single NLR and have greatly advanced our understanding of recognition and subsequent down-stream signalling, they can fall short on taking within population variation and epistatic effects into account.

Thus, systematic studies combining genomic, phenotypic and molecular approaches at different scales (within populations, between populations, on a species level, and between species) are required to truly advance our knowledge on the evolution of specificity.

Figure Legends

Conflicts of interest, acknowledgements, funding information and author contribution

The authors declare that they have no conflict of interest.

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