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REVIEW

Molecular genetics of leaf rust resistance in wheat and barley

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Abstract

The demand for cereal grains as a main source of energy continues to increase due to the rapid increase in world population. The leaf rust diseases of cereals cause significant yield losses, posing challenges for global food security. The deployment of resistance genes has long been considered as the most effective and sustainable way to control cereal leaf rust diseases. While genetic resistance has reduced the impact of these diseases in agriculture, losses still occur due to the ability of the respective rust pathogens to change and render resistance genes ineffective plus the slow pace at which resistance genes are discovered and characterized. This article highlights novel recently developed strategies based on advances in genome sequencing that have accelerated gene isolation by overcoming the complexity of cereal genomes. The leaf rust resistance genes cloned so far from wheat and barley belong to various protein families, including nucleotide binding site/leucine-rich repeat receptors and transporters. We review recent studies that are beginning to reveal the defense mechanisms conferred by the leaf rust resistance genes identified to date in cereals and their roles in either pattern-triggered immunity or effector-triggered immunity.

Introduction

Cereals account for two-thirds of major food crops for humans (Hancock 2004). Rice, wheat, maize, and barley are the four most important cereals, contributing directly to more than half of all calories consumed by humans (Awika 2011). Total cereal production in 2017 was 2.95 billion tonnes, of which the four most important food crops account for 2.82 billion tonnes or roughly 95% of total production (FAOSTAT 2017). World population in 2050 is estimated to exceed 9.1 billion, and the demand for cereals is forecast to reach more than 3 billion tonnes (Elferink and Schierhorn 2016).

Despite shrinking land and water resources, cereal production needs to increase to meet global demand. One of the major agricultural challenges is crops with resistance to diseases that threaten productivity. Genetic improvement through the incorporation of resistance is the most economical, effective, and ecologically sustainable way to control many diseases in plants. However, genetic resistance is often overcome as pathogens evolve matching virulence. Among diseases in cereals, rusts caused by fungal species within the genus *Puccinia* have proven to be a major biotic factor that continues to limit the profitable cultivation of wheat, barley and oat worldwide. Bread wheat (*Triticum aestivum*) and cultivated barley (*Hordeum vulgare* L.) are affected by three main rust diseases: leaf rust, stripe rust, and stem rust. Among them, leaf rust is the most common and prevalent, affecting cereals globally (Clifford 1985; Park et al. 2015), major epidemics being reported in Australia (Murray and Brennan 2010, 2009; Park 2003), New Zealand (Arnst et al. 1979) and the USA (Griffey et al. 1994). Under epidemic conditions, yield losses caused by wheat leaf rust can vary from 15% (Roelfs and Bushnell 1985) to more than 50% if infection occurs at early growth stages (Huerta-Espino et al. 2011), whereas in barley losses to leaf rust can exceed 60% (Clifford 1985; Cotterill et al. 1992; Griffey et al. 1994; Park et al. 2015).

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Globally, the incidence of rust diseases in wheat and barley is minimized using cultivars carrying genetic resistance and fungicides. New resistance genes are often sourced from landraces or related wild species to diversify the resistances in use. Conventionally, new cultivars are generated by crossing or backcrossing of the source line (carrying resistance) with high yielding and desirable varieties (elite lines). However, the process remains tedious due to recurrent cycles of selection of resistance through pathogen screening. The process becomes even more prolonged and complex when selecting for more than one resistance gene.

Isolation of the actual gene responsible for resistance provides the basis to develop a perfect marker to track resistance genes in breeding populations. Furthermore, knowing the molecular determinants underlying crop resistance helps to understand the defense mechanisms more deeply and may lead to the discovery of new strategies to achieve durable disease resistance. The identification of the coding sequences of resistance genes is a precursor for the application of other advanced techniques like the development of resistance gene cassettes (Nuccio et al. 2015) and gene editing in breeding disease-resistant cultivars (Yin and Qiu 2019). In this review, we highlight various strategies that have been developed recently that allow the rapid cloning of disease resistance genes. Emphasis is placed on complexity reduction approaches based on specific baits designed for disease-related genes and the power of next-generation sequencing. We also discuss the various types of resistance mechanisms that cereals have developed during co-evolution with the leaf rust pathogens.

Genetic resistance to leaf rust diseases

In wheat, 79 loci conferring resistance to *P. triticina* have been catalogued (*Lr1* to *Lr79*) (Herrera-Foessel et al. 2014; Park et al. 2014; Qureshi et al. 2018; Singh et al. 2013); in barley, 26 loci confer resistance to *P. hordei* (*Rph1* to *Rph26*) (Kavanagh et al. 2017; Park et al. 2015; Yu et al. 2018; Ziems et al. 2017). Rust fungi are obligate biotrophs (Aime et al. 2017), meaning that they extract nutrients only from living host tissues (Glazebrook 2005). Resistance to leaf rust pathogens in cereals is often divided into seedling resistance (effective at all growth stages of the plant) versus adult plant resistance (effective only at adult plant growth stages), based on the growth stage at which it becomes effective. It can also be grouped into complete resistance (no macroscopically visible symptoms at all), incomplete or intermediate resistance (small rust lesions), and susceptible (rust growth and sporulation are not limited by host), based on the phenotype (Fig. 1). The molecular basis of the individual gene-specific resistance response is largely unknown.

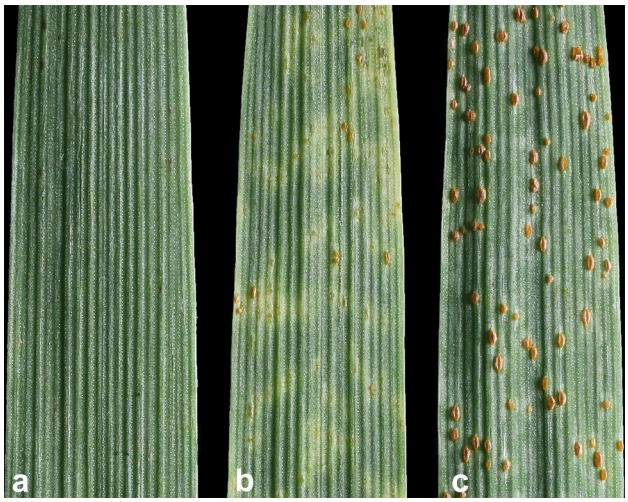

Fig. 1 Types of resistance to leaf rust in barley: **a** complete resistance conferred by seedling gene *Rph18* in barley represented by fleck only, **b** incomplete resistance conferred by seedling gene *Rph3* represented by small pustules surrounded by chlorosis, and **c** susceptibility on barley cv. Gus with large pustules and no signs of chlorosis or cell death surrounding

Genes conferring seedling resistance, also known as all stage resistance (ASR), show incompatible responses in all developmental stages. Although this resistance is often race specific (Parlevliet and Ommeren 1975), the time that such genes remain effective following deployment can differ significantly. For example, barley leaf rust resistance gene *Rph7* remains effective in Europe after being used for more than 20 years (Brunner et al. 2000), but virulent pathotypes have been found elsewhere (Golan et al. 1978; Parlevliet et al. 1981; Steffenson et al. 1993). The durability of a race-specific gene depends upon how extensively the gene in question has been deployed and how widespread the cultivation of varieties carrying that specific gene. Park and McIntosh (1994) documented that release of Australian wheat variety Timgalen (carrying complementary genes *Lr27*+*Lr31*) and its widespread cultivation in 1967 was followed by detection of virulence for *Lr27*+*Lr31* in 1970. Many such corresponding relationships between frequencies of resistance genes of the host and virulence genes in the pathogen (often known as 'boom and bust cycles') have been established globally in wheat and barley, e.g. *Lr24* (Long et al. 2000; Park et al. 2002), *Sr24, Sr36* (Pretorius et al. 2007), and *Rph12* (Park 2008).

Adult plant resistance (APR) genes express only in post-seedling growth stages (Park et al. 2015), and therefore genotypes carrying such resistance are susceptible at the seedling stages (Gupta et al. 2018; Parlevliet and Ommeren 1975). Adult plant resistance is often reputed to be race non-specific, incompletely dominant, and durable (Gupta et al. 2018; Singh et al. 2005). Some APR genes conferring

resistance to cereals rust have been proven to be durable including *Rph20* and *Rph23* in barley (Hickey et al. 2012; Park et al. 2015; Singh et al. 2015) and *Lr34* in wheat (Krattinger et al. 2009). Pathotypes with matching virulence have not been found despite their widespread use in agriculture. On the other hand, race-specific and non-durable APR genes have been reported in wheat, for example *Lr12* and *Lr22b* (Park and McIntosh 1994). Table 1 provides salient features and characteristics of ASR and APR.

Complete resistance is generally conferred by a major resistance gene that shows no visible symptoms when the rust spore lands on the leaf and attempts to penetrate the mesophyll cells. Only a few seedling resistance genes belong to this category such as barley *Rph18* (Park et al. 2015) and wheat *Lr1* (Dyck and Kerber 1985).

Incomplete resistance can be conferred by major or minor genes. It may reduce damage caused by rust pathogens by prolonging the latent period, decreasing pustule size, and delaying spore production, and is in some cases referred to as slow rusting (Ballini et al. 2013; Parlevliet and Ommeren 1975; Singh et al. 2007) (Fig. 1). The level of resistance provided by the deployment of any single, incomplete resistance gene is generally not adequate (Hickey et al. 2011; Marcel et al. 2007; Qi et al. 1998; Singh et al. 2017). In wheat, the effect of wheat leaf rust resistance genes *Lr34, Lr46, Lr67* and *Lr68* is considered to resemble that of incomplete resistance. Martinez et al. (2001) demonstrated that a near-isogenic line of wheat carrying *Lr46* showed longer latency period, decreased colony size and reduced infection frequency compared to its susceptible recurrent parent Lalbahadur. Likewise, Singh et al. (2007) demonstrated that the major role of *Lr34* is the reduction of initial rust increase (via longer incubation period and latent period), thereby minimizing inoculum development through winter and early spring, and subsequently delaying the onset of epidemics. In barley, *Rphq2* sourced from cultivated barley, which may be the same locus as *Rph22*, sourced from *H. bulbosum*, confers incomplete and non-hypersensitive resistance by increasing the latency period (Wang et al. 2019b). Similarly, *Rph26* prolongs the latency period and reduces fungal biomass within infected tissue (Yu et al. 2018).

Isolation of resistance genes

Genomic advancement based on second- and third-generation sequencing has resulted in the availability of reference genomes of over 200 plant genomes. However, the main challenges in genomics are still the association between phenotypic variation and specific nucleotide polymorphisms. DNA changes include: change in coding sequences that result in amino acid change or the introduction of frameshift; change in regulatory elements (*cis* or *trans*) that result in an alteration of gene expression level or location (tissue or time); and modification in DNA methylation that also alters expression pattern (Bevan et al. 2017). The detection of the genomic sequence underlying these traits expands our knowledge of basic physiological and molecular processes in plants and enables plant geneticists to design crops with better performance to serve society (Stein and Muehlbauer 2018). Numerous gene-cloning strategies have been developed based on advances in genomics over the last few years (Bettgenhaeuser and Krattinger 2019) that are summarized below.

Classical map-based cloning

Map-based cloning, also known as positional cloning, is a traditional method to identify the nucleotide change responsible for a specific phenotype. The map-based cloning process exploits the linkage between molecular markers whose physical position in the genome is known and the target phenotype (Jander et al. 2002). Map-based cloning comprises three main steps: (1) generation of genetic map/s based on a bi-parental population to reveal the location of the gene relative to the molecular markers, (2) conversion of the genetic map into a physical map that delimits the region carrying candidate genes in between closest flanking markers, and (3)

Table 1 Types of resistance to leaf rust in cereals and their main features

Resistance	Expression stage	Resistance reaction	Genetics	Inheritance	Race specificity	Durability
Seedling or all stage resistance	Throughout life cycle of the plant	Various degrees of hypersensitive reactions	Usually conferred by single major genes (often dominant)	Mendelian	Race specific	Low
Adult plant resistance	Adult plant growth stages only	Typically[a] non-hypersensitive reactions depending upon number of genes involved	Usually present together in combination with other similar genes	Quantitative	Race non-specific[b]	High

[a]Examples of APR with hypersensitive response available, e.g. *Lr48* and *Lr49* (Saini et al. 2002)

[b]Examples of race specific APR available, e.g. *Lr12* and *Lr22b* (Park and McIntosh 1994)

identification of the nucleotide polymorphisms responsible for the phenotype of interest (Stein and Muehlbauer 2018) (Fig. 2a). Steps 2 and 3 are the most laborious, requiring identification and sequencing of the chromosome segments via constructs such as Bacterial Artificial Chromosome (BAC) clones that harbour the targeted molecular markers (Komatsuda et al. 2007; Pourkheirandish et al. 2015). These two steps have been accelerated in recent times due to the availability of reference sequences of many crops, especially cereals such as wheat and barley (Appels et al. 2018; Mascher et al. 2017).

Isolating genes using the map-based approach can utilize the great resource of natural and induced mutations without prior assumptions or knowledge of specific genes (Jander et al. 2002; Thind et al. 2017). Many genes conferring resistance to diseases in cereal crops were isolated using the positional strategy before the availability of high-quality reference genome sequences of crops, for example, *Mlo* in barley conferring resistance to powdery mildew (Büschges et al. 1997), *Rpg1, rpg4* and *Rpg5* in barley conferring resistance to stem rust (Brueggeman et al. 2002, 2008), *Xa21* in rice conferring resistance to bacterial blight (Song et al. 1995), and *Lr1*, *Lr10* and *Lr21* in wheat conferring resistance to leaf rust (Cloutier et al. 2007; Feuillet et al. 2003; Huang et al. 2003). The availability of reference genome sequences led to a substantial increase in the number of studies on gene cloning in rice and *Arabidopsis,* but not so in the case of wheat and maize (Bettgenhaeuser and Krattinger 2019), likely because of the large and complex genomes of these cereals. The genome resequencing process applied in various cereal crops has generated numerous SNPs that can be used for marker development (Yang et al. 2012). The number of SNPs varies among plant species: in maize, 3.3 million SNPs and INDELs have been found (Gore et al. 2009), 3.6 million SNPs in the rice genome (Huang et al. 2010), and 15 million SNPs in the barley genome have been detected (Mayer et al. 2012).

One of the disadvantages of the map-based cloning strategy is that it is time-consuming, requiring at least three seasons to generate an $F_{2:3}$ segregating population (Bettgenhaeuser and Krattinger 2019) and even more if recombinant inbred lines (RILs) or near-isogenic lines (NILs) are developed to establish the linkage of QTLs to molecular markers (Wang et al. 2019a). However, advances in double haploid production in cereals (Niu et al. 2014) coupled with the application of rapid generation protocols in cereals (Hickey et al. 2017; Sysoeva et al. 2010) have dramatically reduced the time required to develop homozygous progeny (Bettgenhaeuser and Krattinger 2019; Forster and Thomas 2005) and mapping populations. High-density genotyping using numerous molecular markers that are ubiquitous nowadays also reduces the time and workload to develop a saturated linkage map (Rasheed et al. 2017). Another major disadvantage of map-based cloning is its dependence on meiotic

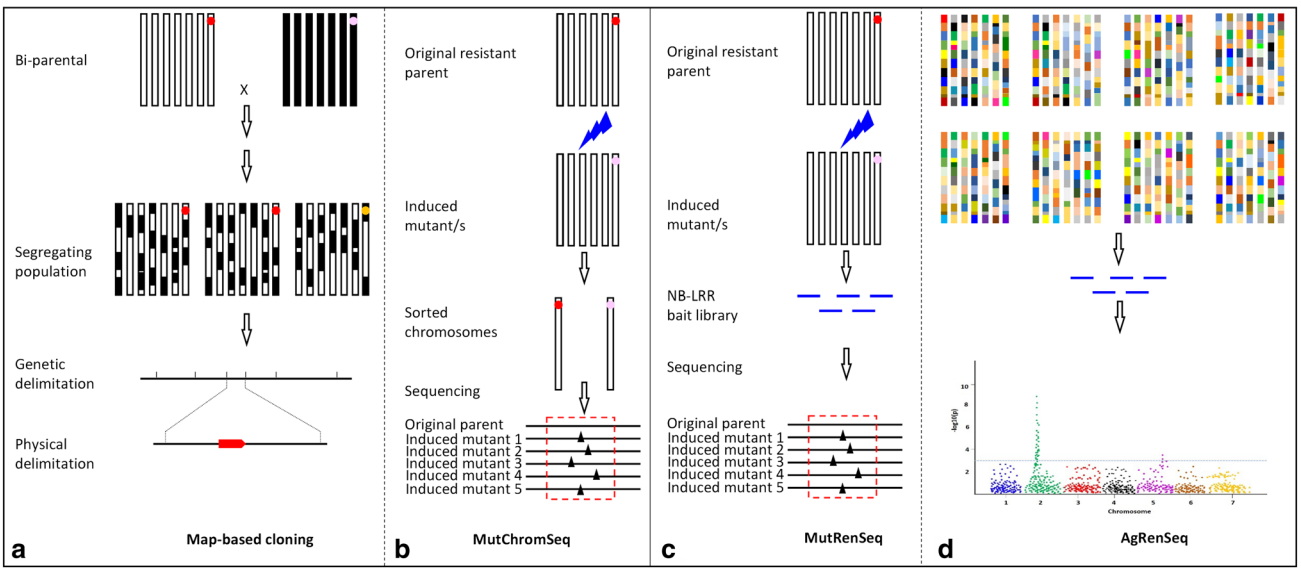

Fig. 2 Various gene-cloning strategies have been used in cereals. **a** The cultivar carrying resistance allele (red dot) is crossed with the cultivar carrying the susceptibility allele (orange dot) to produce F_2 segregating generation. The genetic map is converted into a physical map to search for the candidate gene. **b** The initial map determines the target chromosome (red dot). Induced mutants are produced and selected for loss-of-function followed by chromosome sorting. The chromosome carrying the target gene is sequenced and compared with the wild type sequence to find the causal gene. **c** A bait library is designed for R gene enrichment. The induced mutant and wild type DNAs are captured by NLR baits and sequenced to find the causal NLR gene. **d** A panel of cultivars with and without the desired phenotype is used for genome-wide association analysis combined with NLR bait captures to find the causal NLR (color figure online)

recombination. In regions with reduced meiotic recombination such as the pericentromeric region (near to centromere), a larger F_2 population is required, and in some instances, map-based cloning may even fail as the gene is located in a non-recombining segment of a chromosome (Li et al. 2017).

Mutant chromosome sequencing (MutChromSeq)

Mutagenesis followed by chromosome sorting and then sequencing of the isolated chromosome (MutChromSeq) is a technique that was developed recently to isolate a gene of interest from large genomes such as barley and wheat (Dracatos et al. 2019; Sánchez-Martín et al. 2016). The major steps of this technique include: (1) mutagenesis of a genotype carrying the dominant allele and screening for loss-of-function mutants, (2) flow sorting chromosomes to separate the chromosome carrying the target gene, and (3) sequencing and comparing wild type and induced mutant separated chromosomes to find the candidate gene (Sánchez-Martín et al. 2016) (Fig. 2b). This strategy significantly reduces genome complexity based on the ability to separate a single chromosome by fluorescent labelling of the DNA repeat sequences followed by chromosome flow sorting (Periyannan 2018). In this case, only the chromosome carrying a target gene needs to be sequenced (i.e. one out of seven chromosomes of barley or of the 21 chromosomes of wheat). As a result of sequencing only the target chromosome, the analysis workload, as well as the sequencing cost, is greatly reduced. Gene isolation using this approach nonetheless requires the initial map position of the target gene to identify the target chromosome to be separated by flow cytometry (Dracatos et al. 2019; Sánchez-Martín et al. 2016). In addition, these studies use five to six mutants to identify the candidate gene, meaning that larger mutant populations are required (Mago et al. 2017). However, the use of a suitable concentration of a mutagen can substantially increase the efficiency of screening (Gottwald et al. 2009). The bottleneck of this approach is flow sorting chromosomes, which is a very specialized technique. Consequently, it only can be applied in plants where an individual chromosome can be isolated (Periyannan 2018). Another limitation is mutant allelism (Munoz-Amatriain et al. 2011). Even though mutants with altered phenotypes can be identified by screening, M2 families need further allelism tests to assure that the phenotype is compromised due to the same target gene of interest.

Resistance gene enrichment sequencing (RenSeq)

Resistance gene enrichment sequencing (RenSeq) is a direct cloning method that targets genes containing NLR domains (Jupe et al. 2013). RenSeq uses gene family-specific exome capture through the design of oligonucleotide baits (Jupe et al. 2013) that permit direct comparisons of contrasting alleles (Steuernagel et al. 2016). RenSeq enables rapid identification of genes responsible for resistance without positional mapping. The procedure includes three main steps: (1) design a customized bait library for NLR gene enrichment of the target species, (2) capture DNA with NLR genes, and (3) sequence the captured DNA using high-throughput sequencing platforms such as Illumina. The RenSeq strategy has been deployed along with other techniques to clone plant disease resistance genes (Andolfo et al. 2014; Arora et al. 2018; Kamil et al. 2016).

RenSeq has several advantages over the map-based cloning and MutChromSeq approaches. Firstly, the use of the RenSeq method dramatically reduces genome complexity. This approach only focuses on the largest resistance gene family with NLR domains that accounts for a small proportion of the genome of crops. For instance, approximately 130 genes encode for NLR proteins (Meyers et al. 1999) in a total of 25,498 genes of the whole genome of *Arabidopsis thaliana* (Kaul et al. 2000), while in rice 600 genes encode NLR proteins (Goff et al. 2002) of 37,544 genes in total (Matsumoto et al. 2005). Moreover, the capture and sequencing of long DNA fragments in this technique overcomes repetitive, or structural variation in the genome (Wang et al. 2015) as the long reads may span the repeat-rich regions (Kamil et al. 2016). Secondly, RenSeq is cost-effective (Jupe et al. 2014) as it does not require sequencing the whole genome or even a whole chromosome that has large proportions of repetitive elements, especially in the cereals (Flavell et al. 1977; Mayer et al. 2012; Meyers et al. 2001).

One of the major limitations of RenSeq is the design of oligonucleotide baits. This design can be based on a reference genome sequence (Lee and Yeom 2015), but considering the large-scale presence/absence variations among different accessions, a pan-genome is the ideal reference on which to design baits. Even though advances in next-generation sequencing have boosted the speed, as well as reduced the cost of the whole-genome sequencing (Huang and Marth 2008), the cost of generating pan-genomes is still considerable especially for plant species with large genomes. A second limitation of gene isolation with RenSeq is that it is limited to isolating only resistance genes encoding NLR proteins, meaning that genes that do not belong to the NLR family are missed (Jupe et al. 2013; Kamil et al. 2016; Steuernagel et al. 2016) (Table 2).

Mutagenesis with resistant gene enrichment sequencing (MutRenSeq)

This is a pipeline that uses RenSeq baits in both induced mutants and the original wild type parent. The MutRenSeq strategy, a modified version of RenSeq, was used to clone two genes (*Sr22* and *Sr45*) conferring resistance to stem

Table 2 Comparison of gene isolation strategies

Gene isolation approach	Map-based cloning	MutChromSeq	RenSeq	MutRenSeq	AgRenSeq
Speed	Slow	Very rapid	Rapid	Very rapid	Rapid
Cost-effectiveness	No	No	Yes	Yes	No
Dependent on reference genome	No	No	Yes	Yes	Yes
Multiple gene isolation	No	No	No	No	Yes
Gene mapping required	Yes	Yes	No	No	No
Loss-of-function mutants required	No	Yes	No	Yes	No
Main drawbacks	Depends on recombinations	Chromosome isolation and sequencing	Only useful to isolate NLR genes	Only useful to isolate NLR genes	Only useful to isolate NLR genes

rust in wheat (Steuernagel et al. 2016). In comparison with the original RenSeq, mutagenesis and screening for loss-of-function mutant steps are added. Juxtaposing sequences of enriched DNA from wild type and mutants allows the identification of candidate genes (Fig. 2c). The advantages of the MutRenSeq strategy are time-saving, cost-effectiveness, independence from gene mapping, and its utility in plant species with large genomes (Steuernagel et al. 2016). The disadvantages of RenSeq also apply to MutRenSeq, which is its limitation to genes encoding NLR proteins (Jupe et al. 2013; Kamil et al. 2016; Steuernagel et al. 2016) and the need for a reference pan-genome (Lee and Yeom 2015) to design capture baits. Furthermore, many genes in plants cannot be mutated as they are vital for survival; hence, any approach based on mutagenesis to generate loss-of-function mutants of such genes will lead to lethality.

Association genetics with resistance gene enrichment sequencing (AgRenSeq)

This platform combines genome-wide association scans (GWAS) (Luke et al. 2011) with RenSeq and was used to isolate four genes conferring resistance to stem rust in wheat (*Sr33*, *Sr45*, *Sr46,* and *SrTA1662*) (Arora et al. 2019). The advantage of GWAS is the use of historical recombination, and lower linkage disequilibrium (LD) compared to bi-parental populations. The success of GWAS will depend on the extent of LD in the population, population structure when diverse members are varying for resistance to a group of pathogen isolates, and accurate phenotyping. Due to the use of RenSeq, this technique requires an NLR bait library (and hence is limited to the NLR gene family) and sequencing plus a genome-wide association step (Fig. 2d). On the positive side, this technique reduces genome complexity so that it can be used to isolate resistance genes from crops with large genomes (Steuernagel et al. 2016). The AgRenSeq approach also allows the isolation of multiple resistance genes simultaneously because it is not limited to bi-parental populations or a specific mutant (MutRenSeq); therefore, it is highly cost-effective. The AgRenSeq technique requires sufficient biological material to ensure the genetic diversity of the panel used for GWAS (Arora et al. 2019).

Other approaches for gene isolation

In addition to the gene isolation approaches mentioned above, many other strategies have been used successfully to clone genes conferring important traits in plant species, including MutMap, and its modified version (MutMap-Gap). This platform has been used to isolate mutations conditioning pale green leaves and semi-dwarfism in rice (Abe et al. 2012), and the gene *Pii* conferring resistance to rice blast (Takagi et al. 2013). Gene isolation using the MutMap approach is based on crossing a mutant by its original wild type and the self-fertilization of F_1 plants to generate F_2 plants that segregate for the trait of interest (Abe et al. 2012). In addition, the targeted chromosome-based cloning via a long-range assembly (TACCA) approach was used to identify the *Lr22a* locus in bread wheat (Thind et al. 2017). The TACCA approach is quite similar to the MutChromSeq approach as it is based on mutagenesis and chromosome flow sorting, but differs in using long-range assembly instead of shotgun sequencing.

The introduction of next-generation sequencing technologies at the beginning of the twenty-first century, including Illumina, has allowed over 200 plant genomes to be assembled to date (Chen et al. 2018). The major issue posed by second-generation sequencing technologies was short read length, making genome assembly problematic and sometimes impossible for repetitive sequences, resulting in fragmented assemblies. The introduction of long-read sequencing produced by PacBio and Oxford Nanopore now allows for chromosomal level assemblies of plant genomes (Belser et al. 2018). The recent strategies of gene identification depend on the power of next-generation sequencing for whole-genome sequencing, chromosome sequencing, or genotyping-by-sequencing (GBS). High-density maps of the target loci can be constructed using GBS, and

high-resolution maps are being used to select critical recombination sites close to the target genes. RenSeq enables the rapid identification of genes responsible for disease resistance without fine mapping. Classical bi-parental map-based cloning approaches and GWAS can be used in parallel to avoid excluding genes that do not belong to the NLR family.

Resistance mechanisms to leaf rust in cereal crops

Puccinia hordei and *Puccinia triticina,* the causal agents of leaf rust diseases in barley and wheat, penetrate plant tissue via a germ-tube through the stoma. These pathogens invade the mesophyll cells by modifying the host plasma membrane to form an extrahaustorial membrane that invaginates around the haustorium (Gan et al. 2010). The fungus absorbs nutrients from the plant cell via the haustorium. Two major categories of defense mechanisms in plants are known as basal defense and R-gene mediated defense mechanisms. Basal defense provides resistance to a wide range of pathogens by both non-host and host resistance, whereas R-gene mediated defense provides host resistance and usually responds to specific pathogens (Gururani et al. 2012). Rust pathogens secrete particular proteins called effectors that alter the plant host in a way that is beneficial to the pathogen (Fig. 3). In return, plants have evolved specialized resistance (R) genes, the products of which can detect the presence of specific effectors and trigger the plant immune system (Dodds and Rathjen 2010). Disease resistance in plants takes place in three main stages, viz. pathogen recognition, signal transduction, and defense responses. The plant detects pathogen attack using specific proteins (pathogen recognition) also known as resistance proteins. This detection is followed by signalling to alert the plant's immune system that infection is taking place (signal transduction). Once the parasite is detected, the plant reacts to defend itself against the pathogen (defense response) through various mechanisms, including sacrificing the infected cells or cutting off the nutrient source to the pathogen, and the pathogen eventually starves.

Pathogen recognition

Plant defense mechanisms (basal immunity and R-mediated resistance) are usually triggered by recognition receptors. Pattern recognition receptors (PRRs) are either receptor-like kinases (RLKs) or other receptor-like proteins (RLPs) located on the cell surface that recognize pathogen-associated molecular patterns (PAMPs) (Zipfel 2014) (Fig. 3). However, damage-associated molecular patterns (DAMPs) can be recognized by wall-associated kinases (WAKs) (Decreux and Messiaen 2005). Both RLKs and RLPs are constructed from multi-domains including extracellular ectodomains, transmembranes and cytoplasmic domains (Rathore and Ghosh 2018). The RLKs can trigger signalling cascades based on the long cytoplasmic domain, while RLPs have a small cytoplasmic domain, so they depend on other cytoplasmic proteins to activate downstream signalling. The PRRs activate pattern-triggered immunity (PTI) (Gómez-Gómez and Boller 2002; Kohorn et al. 2012; Segonzac and Zipfel 2011; Zipfel et al. 2004) to provide the first protective layer and protect the plant from most non-adapted pathogens (Zipfel 2014). In *Arabidopsis* spp., the ATP-binding cassette (ABC) transporter protein encoded by the *PEN3* gene is plasma membrane localized and supposed to be involved in the secretion of antifungal products into the apoplast (He et al. 2019; Stein et al. 2006). The wheat leaf rust resistance gene *Lr34* also encodes an ABC transporter (Krattinger et al. 2009) and is suggested to have similar function. In barley, the leaf rust resistance gene *Rph22* encodes a lectin receptor kinase, a member of a protein family located in the plasma membrane (Wang et al. 2019b) and perceives extracellular ATP (Tanaka et al. 2014), 3-hydroxy fatty acid metabolites (Kutschera et al. 2019) and peptides (Bouwmeester et al. 2011). One of the well-known PAMPs is chitin (Boller 1995), a ubiquitous component of the cell wall of fungal pathogens including rust fungi (Kendrick 2017); the detection of chitin triggers defense responses in plants (Shibuya and Minami 2001). In rice, CEBiP binds chitin at the cell surface to form a complex that requires one specific RLK to induce signalling as CEBiP by itself has no functional intracellular domains (Kaku et al. 2006; Miya et al. 2007).

Plant cells have intracellular-localized receptors that directly or indirectly recognize effectors generated by pathogens during invasion (Dangl et al. 2013) and activate the second layer of the plant defense system (so-called effector-triggered immunity; ETI) (Zipfel 2014). Most of these receptors are NLR proteins (Dodds and Rathjen 2010; Zipfel 2014), and they recognize pathogen effectors via LRR domains (Padmanabhan et al. 2009). The recognition of pathogen effectors via direct interaction with NLR protein receptors has been reported in several leaf rust resistance genes in wheat and barley such as *Lr1*, *Lr21* and *Rph1* (Cloutier et al. 2007; Dracatos et al. 2019; Huang et al. 2003), and these proteins are likely to play a role as receptors that recognize the pathogen effectors directly (Fig. 3). In indirect recognition, NLR receptors monitor the status of specific host proteins and any modifications to these monitored targets (also known as guardees or decoys) caused by a pathogen effector will activate those receptors (Sarris et al. 2016; van der Hoorn and Kamoun 2008). For instance, two NLR receptors in *Arabidopsis thaliana*, RPS2 and RPM1, monitor the status of the protein RIN4 and detect modification of RIN4 caused by effectors AvrRpt2 and AvrRpm1 generated by *Pseudomonas syringae* (Andersson et al. 2006; Axtell et al. 2003; Mackey et al. 2002). The protein encoded by

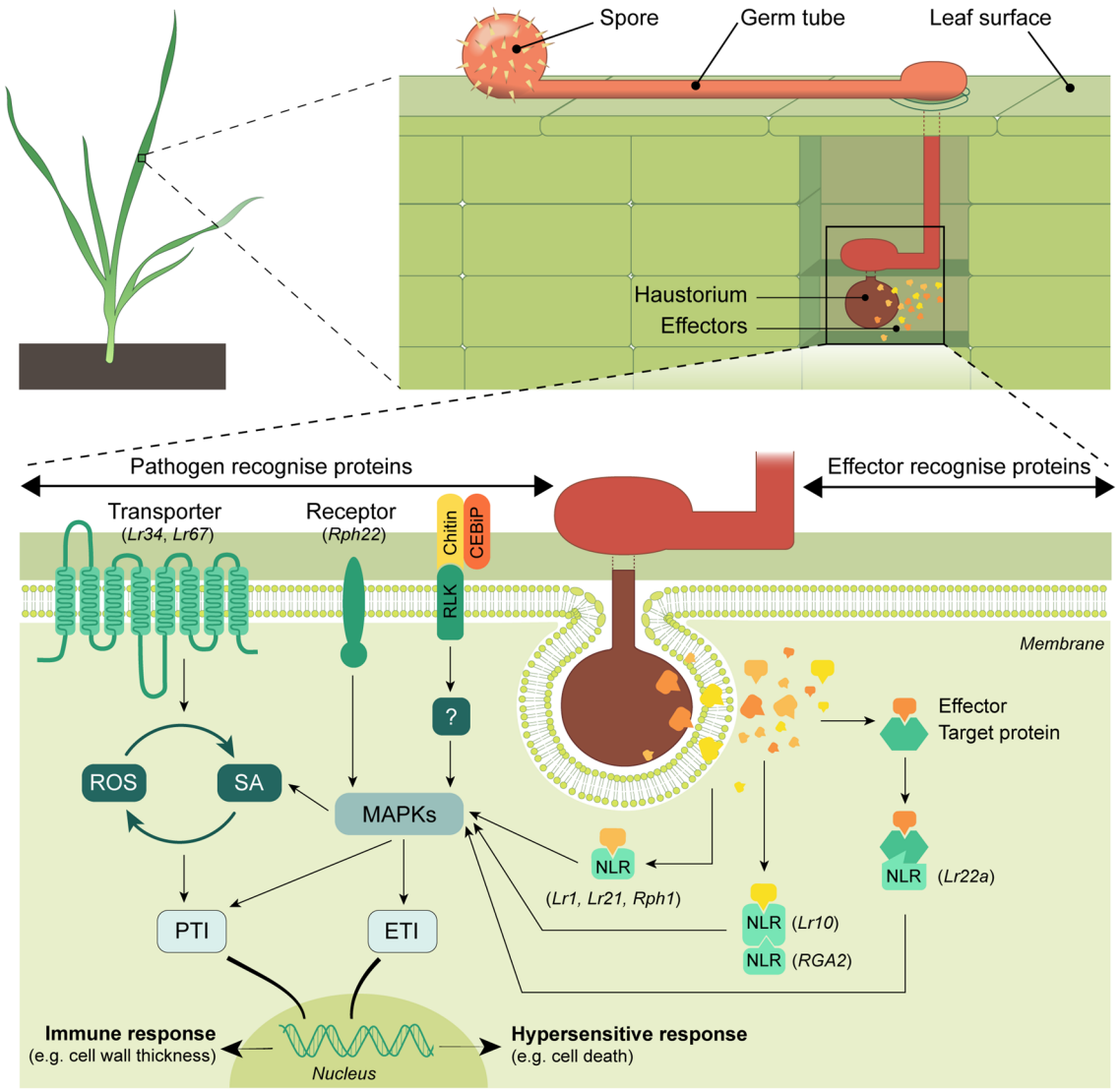

Fig. 3 Resistance mechanisms to leaf rust disease in cereals. The efforts to penetrate the mesophyll cells of rust spores cause some alterations in the cell surface (PAMPs/DAMPs) that can be recognized by transporters (*Lr34* and *Lr67*) and receptor kinase (*Rph22*) located on the cell membrane. Chitin in the cell wall of fungi binds to CEBiP to form a complex that is recognized by a receptor-like kinase (RLK). These molecules then trigger various signalling cascades with the involvement of MAPKs, ROS, and/or SA to induce defence responses. The specific structure penetrates the mesophyll cells via a membrane, and they release effectors via haustoria. The NLR proteins recognize the effectors directly (*Lr1*, *Lr21,* and *Rph1*), indirectly (*Lr22a*), or work in pairs (*Lr10* and RGA2). The recognition is followed by MAPKs cascade to trigger both tiers of the defence system (PTI and ETI)

the wheat leaf rust resistance gene *Lr22a* shows a high level of amino acid identity with the *Arabidopsis* protein RPM1 (Thind et al. 2017). Thus, it is very likely that this protein also recognizes a pathogen effector indirectly. In wheat, both NLR coding genes *Lr10* and *RGA2* are required for leaf rust resistance regulated by the *Lr10* locus (Loutre et al. 2009) and this resistance may be mediated by the guard model. Moreover, the sequence of *Lr10* is highly diverse, while that of *RGA2* is much more conserved, and these facts suggest that *Lr10* may act as the guardee and directly interact with the effectors while RGA2 acts as a guard (Fig. 3). The recognition of pathogen effectors in an indirect manner was reported to be more complex in other proposed models such as the integrated decoy (Cesari et al. 2014) or integrated sensor (Wu et al. 2015) models.

Signal transduction

The process from pathogen recognition to defense response occurs through an intermediate process, called signalling transduction (Padder 2014); this process is activated when the pathogen is detected by the host via receptor proteins

or effectors are detected within the cell. Various signalling cascades have been found to deploy proteins or phytohormones to transmit the detected signals to the host's defense system (Fig. 3).

One of the most important groups of proteins involved in signalling is the NLR (Tameling and Joosten 2007). The NLR proteins in plants can be divided into two groups, including CNLs (CC-NLR proteins) and TNLs (TIR-NLR proteins) based on the presence of a Coiled-coil or Toll-like/Interleukin 1 domain in the N-terminus of the protein molecule (Borrelli et al. 2018). The CNLs are found in both monocots and dicots, while the TNLs exist in dicots only (Jacob et al. 2013), suggesting that they evolved after the divergence of monocots and dicots. In the absence of the pathogen, most CNLs are in an inactive form but upon the recognition of pathogen specific effector molecules, they are converted into an active form through intramolecular alterations. The active form thus induces downstream signalling and the cell death response to prevent pathogen proliferation (Casey et al. 2016; Cesari et al. 2016; Maekawa et al. 2011).

The signalling cascade is also regulated by mitogen-activated protein kinases (MAPKs) (Meng and Zhang 2013). MAPKs are critical elements of the plant innate immune system (Galletti et al. 2011), and MAPK cascades are involved in both PTI (Chisholm et al. 2006; Dodds and Rathjen 2010; Kohorn et al. 2012) and ETI (Oh and Martin 2011; Pedley and Martin 2005). MAPK signalling is induced by the PRRs or WAKs based on the recognition of PAMPs and DAMPs for activating PTI. The signalling cascade regulated by the protein encoded by leaf rust resistance gene *Rph22* in barley remains unknown (Wang et al. 2019b), but its closest homolog, *Arabidopsis* LecRK-IX.2, was shown to trigger the MAPK cascade right after the recognition of flg22 (dit Frey et al. 2014). In addition, the MAPK genes, including MAPKKKε and MAPKKKα were found to be involved in downstream signalling pathways of NLR receptors in tomato (del Pozo et al. 2004; Melech-Bonfil and Sessa 2010). Likewise, the NLR proteins encoded by leaf rust resistance genes in wheat and barley such as *Lr1*, *Lr10*, *Lr21,* and *Rph1* may operate upstream of MAPK cascade in signal transduction.

Many different hormones are involved in host–pathogen interactions as a part of the signal transduction step. Among them, salicylic acid (SA) has an extensive signalling role in disease resistance (Vlot et al. 2009), and is considered a critical signal that activates both basal resistance (DebRoy et al. 2004; Kohorn et al. 2012) and effector-triggered immunity (ETI) (Venugopal et al. 2009). This implies that SA may be involved in the signalling pathways of leaf rust resistance regulated by CNL genes including *Lr1*, *Lr10*, *Lr22a* in wheat (Cloutier et al. 2007; Feuillet et al. 2003; Thind et al. 2017) and *Rph1* in barley (Dracatos et al. 2019). Salicylic acid also was found to trigger the expression of pathogenesis-related gene 1 (*PR-1*) to provide resistance to powdery mildew in barley (Muradov et al. 1993) and also induces the expression of pathogenesis-related genes in wheat (Anand et al. 2003). Other hormones involved in signal transduction include jasmonic acid, abscisic acid, nitric oxide, gibberellin, auxin, brassinosteroids, ethylene, and cytokinins (Andersen et al. 2018). The ABC transporters are an important component in different molecular processes in plant cells with the involvement of phytohormones such as abscisic acid or SA (Eichhorn et al. 2006; Kang et al. 2010) that are common in signalling pathways in plant innate immunity (Kachroo and Kachroo 2012; Vidhyasekaran 2015). This implies that the ABC transporter encoded by *Lr34* functions upstream of signalling pathways with the involvement of phytohormones.

The defense response

The defense system in plants may respond in different ways to prevent further infection once the danger signal from a pathogen effector is transmitted. One of the most common responses to plant pathogens is a hypersensitive response (HR) that usually causes programmed cell death (PCD) surrounding the infection (Andersen et al. 2018). Sacrificing the infected cells in this way cuts the energy supply to the invader, resulting in pathogen starvation. PCD is considered an effective resistance strategy against obligate biotrophic pathogens like the causal agents of leaf rust in cereals (Andersen et al. 2018). Among the resistance genes to leaf rust in cereals cloned so far, most encode NLR proteins (Cloutier et al. 2007; Dracatos et al. 2019; Feuillet et al. 2003; Huang et al. 2003; Thind et al. 2017) (Table 3). The activation of NLR proteins usually induces PCD or produces reactive oxygen species (ROS) in plants (Andersson et al. 2006; Qi and Innes 2013). Thus, a hypersensitive response via PCD is likely to be the way in which these genes confer resistance to leaf rust in wheat and barley. In addition, the production of ROS was found to activate PCD (Levine et al. 1994) and adaptation to the environment to make it unfavourable for the development and reproduction of pathogens (Lamb and Dixon 1997).

The non NLR genes may deploy strategies other than PCD to prevent further infection. The ABC transporter encoded by *Lr34* belongs to the protein family that was found to be involved in providing non-host resistance in *Arabidopsis* (Campe et al. 2016). Furthermore, non-host resistance is based on basal resistance through the recognition of PAMPs (Nuernberger and Lipka 2005) and may explain the wide spectrum and durability of the resistance provided by *Lr34* (Krattinger et al. 2009; Mccallum et al. 2017). Similarly, another wheat leaf rust resistance gene, *Lr67*, encodes a hexose transporter (Moore et al. 2015). It is believed that the increase in the hexose/sucrose ratio in the leaf apoplast caused by the blocking of apoplastic hexose retrieval activates the sugar-signalling cascade that leads to

Table 3 List of leaf rust resistance genes isolated in wheat and barley

Locus name	Crop disease	Causal agents	Chromosomal location	Gene type	Protein encoded	Gene isolation approach used	References
Lr1	Wheat leaf rust	*P. triticina*	5DL	Seedling	CC-NBS-LRR	Map-based cloning	Cloutier et al. (2007)
Lr10	Wheat leaf rust	*P. triticina*	1AS	Seedling	CC-NBS-LRR	Map-based cloning	Feuillet et al. (2003)
Lr21	Wheat leaf rust	*P. triticina*	1DS	Seedling	CC-NBS-LRR	Map-based cloning	Huang et al. (2003)
Lr22a	Wheat leaf rust	*P. triticina*	2DS	Seedling	CC-NBS-LRR	TACCA	Thind et al. (2017)
Lr34	Wheat leaf rust	*P. triticina*	7DS	APR	ABC transporter	Map-based cloning	Krattinger et al. (2009)
Lr67	Wheat leaf rust	*P. triticina*	4DL	APR	Hexose transporter	Map-based cloning	Moore et al. (2015)
Rph1	Barley leaf rust	*P. hordei*	2HS	Seedling	CC-NBS-LRR	MutChromSeq	Dracatos et al. (2019)
Rph22	Barley leaf rust	*P. hordei*	2HL	Seedling	Lectin receptor kinase	Map-based cloning	Wang et al. (2019b)

the formation of unfavourable conditions for the development of a pathogen (Proels and Hückelhoven 2014; Sonnewald et al. 2012). Barley leaf rust resistance gene *Rph22* encodes lectin receptor-like kinases that are known to trigger PTI to protect the barley plant (Luo et al. 2017; Wang et al. 2019b). Previous studies showed that LecRKs initially recognize flag22 and activate MAPK at an early stage (dit Frey et al. 2014), and later, the activation of another PTI response leads to the accumulation of callose that plays a role as a physical barrier (Kim et al. 2005).

Cloned leaf rust resistance genes

Of the 100+ loci conferring resistance to leaf rust in wheat and barley, only a few have been isolated: *Lr1*, *Lr10*, *Lr21*, *Lr22a*, *Lr34,* and *Lr67* in wheat, and *Rph1* and *Rph22* in barley. Five of these genes (*Lr1*, *Lr10*, *Lr21*, *Lr22a*, and *Rph1*) confer seedling resistance (race-specific) and encode NLR proteins. Genes *Lr34* and *Lr67* confer adult plant resistance (non-race specific) and encode transporter proteins. *Rph22* is a seedling resistance gene that encodes a lectin receptor-like kinase. No NLR sequence was found in the physical contig of race-specific resistance genes *Rph3* (Dinh et al. unpublished data) and *Rph7* (Scherrer et al. 2005). These results suggest that many resistance genes do not belong to the NLR gene family and that using approaches such as the RenSeq derived method will miss those target genes.

Identification of genes underlying wheat and barley leaf rust resistance will open a window to understanding the molecular function of this class of resistance genes and the discovery of defense mechanisms in cereals. If the isolated gene belongs to the NLR gene family, it will be useful to identify effectors that would enable an understanding of the mechanism by which the pathogen escapes detection by plant immune receptors. If an isolated resistance gene is of a different class of gene, it will expand our knowledge of plant-pathogen defense biology and offer more strategies for rust control.

Future prospects

New strains of pathogens like the rusts continue to evolve. One of the most important factors contributing to the rapid evolution of rust fungi is the diverse sources of genetic variation that may be generated via random mutations in clonal lineages, sexual recombination between different races, and somatic hybridization (Park et al. 2015). Cloning genes that control resistance to rust pathogens will significantly advance our understanding of the molecular components underlying disease resistance and immunity in cereals. Such insight into the molecular mechanisms will be the first step towards the functional characterization of the cereal-rust interaction and allow engineering of new resistance via processes such as allele mining and genome editing. Allele mining of genes isolated from natural populations will identify further functional alleles and illuminate our understanding of the constant struggle between plant and pathogen. Mining genetic diversity will result in the identification of several functional alleles with different specificities that enable us to engineer resistance.

Precision modification of genomes is now possible using Genome editing techniques such as CRISPR-Cas9. Known genes controlling important traits can be selectively modified using genome editing, allowing for the manipulation of phenotypes. As an example, it has been demonstrated that a single amino acid substitution (Arg144Gly) in a hexose transporter in wheat results in the gene *Lr67* conferring resistance. This amino acid substitution evolved recently after common wheat polyploidization. Introduction of the *Lr67* transgene into barley conferred seedling and adult plant resistance to the barley leaf rust pathogen (Milne et al. 2019; Moore et al. 2015). The orthologue sequence of *Lr67* exists in the barley genome, hence altering the Arg144Gly

by genome editing would be expected to produce resistance to rust in barley. The study on the resistance conferred by *Rph22* showed the potential of using resistance genes from related wild species to control diseases in cultivated cereals (Wang et al. 2019b). Similarly, many homologues/orthologues of the isolated genes exist in related species. Isolating a rust resistance gene from one species can provide deeper insight into rust resistance across the cereals, including wheat, barley, rye, oat, and more and an opportunity to edit the genome of related species to create the resistant protein.

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Author Contribution statement MP and RP conceived the review. HD and MP wrote the review. All authors jointly designed, drafted and finalized this editorial.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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