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REVIEW ARTICLE

Contribution of recent technological advances to future resistance breeding

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Abstract

The development of durable host resistance strategies to control crop diseases is a primary need for sustainable agricultural production in the future. This article highlights the potential of recent progress in the understanding of host resistance for future cereal breeding. Much of the novel work is based on advancements in large-scale sequencing and genomics, rapid gene isolation techniques and high-throughput molecular marker technologies. Moreover, emerging applications on the pathogen side like effector identification or field pathogenomics are discussed. The combination of knowledge from both sides of cereal pathosystems will result in new approaches for resistance breeding. We describe future applications and innovative strategies to implement effective and durable strategies to combat diseases of major cereal crops while reducing pesticide dependency.

Introduction

Barley (*Hordeum vulgare*), rice (*Oryza sativa*), rye (*Secale cereale*) and bread wheat (*Triticum aestivum)* are small-grain cereal crops of the *Poaceae* grass family whose domestication and cultivation facilitated the establishment of sedentary agrarian societies, nourishing humankind ever since (Shiferaw et al. 2013). However, diseases caused by a myriad of pathogens reduce cereal yields by 13% annually at the global level (Oerke 2006). Plant disease control is a necessity, not only for economic reasons but also to ensure global food security. Diseases can cause major crop failures triggering food shortages and, occasionally, alter the course of humankind by causing devastating famines (Chakraborty and Newton 2011).

Crop disease management has been mainly achieved through cultural measures (Hobbs et al. 2008), pesticides (Cooper and Dobson 2007) and resistance breeding (Dangl et al. 2013). Cultural practices may reduce disease incidence, but they show limitations (Jørgensen et al. 2014) leaving pesticides and resistance breeding as the genuinely effective practices combating cereal diseases. However, pesticides compromise biodiversity and ecosystem function (Dormann et al. 2007), threatening also human health (Enserink et al. 2013). In addition, pathogens and pests are increasingly showing pesticide resistance (Lucas et al. 2015). Consequently, policymakers seeking low pesticide-input agricultural production systems are formulating more stringent pesticide regulations, especially in Europe (Lamichhane et al. 2015). Therefore, crop disease management through disease-resistant varieties will play a capital and increasingly important role in ensuring future global food security and the relevance of resistance breeding and its underlying research is likely to increase massively.

The benefits of using disease-resistant varieties are manifold. First, they reduce direct yield losses. Second, their use is an environmental-friendly measure to reduce pesticide dependence. Third, such varieties expand the adaptability of crops to areas previously limited by high disease incidences. Fourth, their use in agriculture commonly does not result in additional costs, which is particularly attractive in regions where low-income farmers cannot afford pesticides. Finally, it is a worthwhile investment. For example, the benefit/cost ratio of developing leaf rust-resistant wheat varieties by CIMMYT was 27 times the initial outlay (Marasas et al. 2004).

A wide-ranging review covering resistance breeding in the four main small-grain cereal crops would go beyond the scope of this article, although crop-specific examples are incorporated when instructive. Instead, we aim at increasing awareness of current possibilities in resistance breeding

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and at describing possible future applications and strategies. Here, after briefly revisiting the plant immune system, we present recent progress in genomics and high-throughput genotyping technologies (HTGT) identifying host (resistance gene cloning, genetic diversity assessment, etc.) as well as pathogen factors (avirulence gene identification, field pathogenomics, etc.), which when combined shed light on the molecular function of host-plant interactions. We then discuss how the deeper understanding in host-plant interactions supports the implementation of rational strategies for crop disease control through host resistance. This article will hopefully stimulate discussions on future strategies to devise durable pathogen control strategies improving agricultural yields while promoting sustainability.

All components of the plant immune system are useful for resistance breeding

The plant immune system relies on two main classes of receptors to recognize potential intruders and protect plants against pathogen invasion. The first class consists of membrane-spanning pattern-recognition receptors (PRRs) that recognize evolutionarily conserved pathogen- (or microbial)-associated molecular patterns (PAMPs/MAMPs) leading to PAMP-triggered immunity (PTI). Importantly, due to the conserved nature of PAMPs, PTI plays an important role against non-adapted microbes, known as non-host resistance (NHR), and adapted pathogens in partially resistant/susceptible hosts, termed basal resistance (Zipfel 2014; Couto and Zipfel 2016). In non-host resistance, all genotypes of a species are resistant to all genetic variants of a (non-adapted) pathogen species (Heath 2000), which in turn can infect a more or less closely related plant species (Schulze-Lefert and Panstruga 2011). Basal resistance was defined by Jones and Dangl (2006) quantitatively as a defense that is often a manifestation of residual levels of PTI, inhibiting spread after successful infection of adapted pathogens (Niks and Marcel 2009; Poland et al. 2009; Roux et al. 2014). This basal resistance is, mainly, what breeders have traditionally called quantitative disease resistance (QDR) and is present in most, if not all, plant pathosystems (Parlevliet 1992). QDR is usually controlled by several genes associated with genomic regions called quantitative trait loci (QTL). QDR leads to an incomplete phenotypic resistance, following a near-continuous distribution of phenotypes (from very susceptible to very resistant), resulting from the effects of each gene acting—with small or larger effects—at different stages of the pathogen infection process, leading to a reduction rather than an absence of the disease (Niks et al. 2015). On the other hand, host-adapted pathogens might be able to completely suppress PTI by producing and secreting effector proteins into host cells, allowing infection, resulting in effector-triggered susceptibility (ETS) (Jones and Dangl 2006; Dodds and Rathjen 2010). In turn, these effectors can be recognized, directly or indirectly, by host intracellular receptors encoded by resistance (*R*) genes, leading to effector-triggered immunity (ETI) that usually results in a hypersensitive response (HR) at the infection site, without affecting surroundings cells, whereas host cells retain viability during PTI (Jones and Dangl 2006). PTI and ETI were initially considered as mostly independent layers in the zig-zag model of plant immunity proposed by Jones and Dangl (2006). However, this first assumption has been challenged by recent studies showing that there is no strict PTI/ETI dichotomy. For instance, HR is not restricted to ETI, the differentiation between PAMPs and effectors sometimes cannot be made or PRRs and resistance proteins encoded by *R* genes belong to the same protein classes; we will discuss below the case of the *Stb6* gene of wheat that was identified as a major *R* gene but found to encode a plasma-membrane receptor-like protein, similar to the receptors involved in PTI. Moreover, network analyses have pointed out that PTI and ETI overlap with common events in downstream signaling, such as mitogen-activated protein kinase (MAPK) signaling, reactive oxygen species (ROS) production or hormone signaling, where induced responses are transient in PTI and prolongated in ETI (Tsuda and Katagiri 2010) and the amplitude of those responses is likely dependent on the level required for effective immunity (Thomma et al. 2011). All these discoveries indicate that there is a continuum between PTI and ETI based on the sharing of common signaling machinery, but used differently in PTI- and ETI-based immune responses. The reader is referred to the excellent reviews written by Thomma et al. (2011), Tsuda and Katagiri (2010) or Cook et al. (2015) for a more comprehensive view on this topic. In the last years, great progress has been made in elucidating the molecular mechanisms underlying PTI-, QDR- and ETI-based resistance thanks to the isolation of many of the genes that control these resistance responses. All well-defined plant PRRs are membrane-localized receptor-like kinases (RLKs) (Monaghan and Zipfel 2012) or wall-associated kinases (WAKs) (Hurni et al. 2015). The activation of PRRs leads to activation of mitogen-activated protein kinases (MAPKs) and calcium-dependent protein kinases (CDPKs), two convergent hubs downstream of PRRs that are involved in PTI transcriptional reprogramming and might be the targets of pathogen effectors to hijack PTI signaling pathways leading to susceptibility (Macho and Zipfel 2014). For the case of ETI-based resistance, most of the *R* genes cloned so far encode nucleotide-binding domain leucine-rich repeat containing (NLR) proteins, although the growing number of *R* genes isolated demonstrates that they are much more structurally diverse than originally thought (Cesari 2018). Finally, the picture is more complicated with regard to QDR, as illustrated by the (few) cloned genes so far, which exhibits

a broad range of molecular functions (Poland et al. 2009; Niks et al. 2015). Some of the causal genes are involved in pathogen recognition [altered or weak forms of canonical *R* genes like *Pi35* (Fukuoka et al. 2014) or PRRs as *Xa21* (Pruitt et al. 2015)], transporters, such as *Lr34* (Krattinger et al. 2009) or *Lr67* (Moore et al. 2015a), host metabolism [*Yr36* (Fu et al. 2009) or *Stv11* (Wang et al. 2014a)] or defense [*Pi21* (Fukuoka et al. 2009) or *mlo* (Büschges et al. 1997)]. Thus, molecular mechanisms underlying QDR show a broader mechanistic basis compared to ETI-based resistance. Genes controlling PTI, QDR and ETI responses are valuable genetic resources that have been employed, with varying degree of success, use and acceptance, during decades in resistance breeding. In the following, we briefly mention some of past achievements and strategies employed in traditional resistance breeding using these genetic resources.

R gene-based resistance results in strong and mostly complete resistance (if the *R* gene is not overcome in the pathogen population), translating to an easily scorable phenotype, whereby this type of resistance has been very popular in breeding programs during decades (McDowell and Woffenden 2003). However, as *R* gene-mediated resistance exerts a high selection pressure on populations toward virulence, in many cases *R* genes are quickly overcome (Brown 2015). Thus, *R* gene-mediated resistance tends to be short-lived particularly when deploying varieties with only one resistance gene (McDonald and Linde 2002). Combining multiple *R* genes, "pyramiding" in breeding terms, has been proposed as a strategy to increase the durability of *R* gene-based resistance (Pink 2002) as the likelihood of simultaneous mutations of multiple effectors is low (McDonald and Linde 2002). Besides, *R* genes with different, but complementary resistance spectra, could be combined providing gene pyramids with resistance to a broad set of pathogen races. Pyramiding of *R* genes has been based on phenotyping or marker-assisted selection (MAS), which has resulted in the release of many cultivars widely cultivated (Ellis et al. 2014). However, it is important to remember that the appearance of multivirulent pathogen populations can jeopardize the effectiveness of gene pyramids (Brown 2015), which has made plant breeders reticent to use this strategy in their breeding programs. Nevertheless, new genetic and genomic technologies offer the opportunity of incorporating *R* gene-based resistance in a multitiered strategy combined with other types of resistance to enhance resistance in crops (Zhang and Coaker 2017).

Since PAMPs/MAMPs are conserved and essential for pathogen viability and some PRRs have proven to exhibit broad taxonomic functionality, NHR has been recently seen as a promising resistance breeding strategy to achieve durable and broad-spectrum resistance through the heterologous expression of PRRs (Lacombe et al. 2010; Wulff et al. 2011). Besides, the naturally occurring functional diversity present in crops such as rice (Ayliffe et al. 2011), barley (Atienza et al. 2004) or wheat (Rodrigues et al. 2004) opens up the door to use NHR in resistance breeding in cereal crops, although its practical use in breeding programs is still in an early stage (Bettgenhaeuser et al. 2014; Lee et al. 2016; Elmore et al. 2018). Biotech-based approaches have already proven the applicability of NHR. For example, the maize *Rxo1* gene provides resistance to bacterial leaf streak when transferred to rice (Zhao et al. 2005) or the wheat *Lr34* does likewise against mildew and rust when transferred to barley (Risk et al. 2013). Non-transgenic approaches based on mutation screening and traditional hybridization with close and interfertile species have been practiced with considerable success, for example, in barley using *Hordeum bulbosum* as a donor of NHR against important barley diseases (Shtaya et al. 2007; Johnston et al. 2013).

Although QDR only confers partial resistance, it is of high practical importance in resistance breeding because it is associated with two features very attractive to breeders: broad-spectrum and durable. Because QDR, contrarily to *R* gene-mediated resistance, does not rely on the recognition of rapidly evolving pathogen effectors, QDR is usually effective against all pathogenic races (Lagudah 2011). Besides, several studies have reported QDR as more durable compared to *R* gene-mediated resistance (Parlevliet 2002; Niks et al. 2015). As QDR is controlled by multiple genes with partial and inconsistent effects, the overcoming by one pathogen variant of one (or even few) of those genes does not confer a significant evolutionary advantage over other pathogen races (Poland et al. 2009). This is the reason why QDR has been proposed as a strategy to achieve stable, broad-spectrum and long-lasting resistance to crop diseases (McDonald and Linde 2002). This is of particular relevance in the current context of emerging epidemics, ever-changing pathogen populations and human-driven spread of pathogens (Velásquez et al. 2018). *R*-mediated resistance is race-specific and protects crops against a particular effector repertoire present in some pathogen races, whereas QDR is non-race-specific and confers (partial) resistance against all pathogenic races. Therefore, some authors assume that QDR will play an essential role to control epidemics (Roux et al. 2014).

The phenotype exhibited by genotypes with QDR is the sum of the positive and negative alleles across multiple genes (Corwin and Kliebenstein 2017). A single genotype will only rarely have all favorable alleles that exist in the gene pool. However, breeding allows the development of genotypes containing many favorable allelic variants thanks to transgressive segregation: there, progeny of a cross between two genotypes, intermediately resistant or even partially susceptible, exhibit novel or extreme phenotypes compared to the parental lines resulting from epistatic interactions between complementary, but different,

genes present in the parental lines (Rieseberg et al. 1999). Transgressive segregation is a widespread phenomenon in nature, present in almost any parental combination tested, and, unlike heterosis, heritably stable. Breeders have taken advantage of transgressive segregation to move polygenic resistance into elite varieties by means of recurrent selection (cycles of intercrossing genotypes and selection against highest susceptibility) (Wallwork and Johnson 1984; Parlevliet and van Ommeren 1988) or actively selecting the accumulation of minor genes conferring resistance, the so-called purposeful selection (Parlevliet et al. 1985; Parlevliet and Kuiper 1985). CIMMYT breeders have adopted a "single backcross-selected bulk" scheme (Singh and Trethowan 2007) as a breeding system to produce wheat varieties with near-immunity to rusts by combining in single genotypes multiple minor genes involved in QDR (Singh et al. 2014).

While *R* gene-mediated resistance has mostly benefited from recent technological advances (e.g., MAS or new gene cloning approaches), QDR was affected to a lesser extent. The polygenic nature underlying QDR has hampered MAS due to the low precision of markers estimating QTL effects (Dekkers and Hospital 2002). Indeed, the application of MAS for breeding QDR has been far less effective than phenotypic selection (St.Clair 2010). Nevertheless, commercial breeders have considerably elevated the levels of QDR in their germplasms by phenotypic selection under field conditions (Parlevliet and van Ommeren 1988; Niks et al. 2015). Reliable phenotyping complemented with methods involving different MAS approaches has only been applied in transferring major-effect QTLs similarly to what has been done for qualitative genes (reviewed in St.Clair 2010). However, none of those MAS techniques has proven effective in tracking multiple minor-effect QTLs in a single genotype. Very recently, genomic selection (GS), initially proposed by Meuwissen et al. (2001) to capture the total genetic variance in complex quantitative traits controlled by using whole-genome marker profiles has been suggested as a strategy to effectively predict and select for QDR (Poland and Rutkoski 2016). The ever-decreasing costs of NGS technologies allow the availability of genome-wide markers that can be used to elaborate whole-genome prediction models to better capture all small-effect loci involved in QDR, a trait whose genetic complexity was not captured in the past with few markers through MAS approaches (reviewed in Poland and Rutkoski 2016).

Resistance gene identification: novel genes are needed

When breeding for resistance against cereal diseases, every genetic resource available should be used. Both *R*- or QDR-mediated resistance are highly useful and are not mutually exclusive—rather, they are complementary. In the following, we propose the way forward on the efficient identification and isolation of both types of genes.

Genebanks: treasures of genetic diversity waiting to improve resistance breeding

Genebanks curate diverse plant genetic resources (PGR) encompassing hundreds of thousands of accessions of crop wild relatives, old landraces and local cultivars (Crop Trust 2018). These accessions represent an immense source of genetic variation for resistance breeding (Hajjar and Hodgkin 2007; McCouch et al. 2013) and much of their genetic diversity has not been used in breeding as specific case studies have revealed (Müller et al. 2018). Therefore, it is highly likely that PGR harbor a complete set of "old," mostly uncharacterized resistance genes that may support resistance breeding. Indeed, PGR have already contributed to resistance breeding in two important ways. Firstly, allele mining on previously cloned resistance genes has identified novel functional allelic variants of, just to name a few, *Mla* (a barley powdery mildew resistance gene) (Seeholzer et al. 2010), *Pm3* [a wheat powdery mildew resistance gene (Yahiaoui et al. 2004; Srichumpa et al. 2005; Yahiaoui et al. 2006; Bhullar et al. 2009; Yahiaoui et al. 2009; Bhullar et al. 2010a, b)] or *Pi54* [a rice blast resistance gene, (Vasudevan et al. 2015)]. The combination of such alleles in a single genetic background through transgenic approaches or deployment in multilines has shown to improve resistance in the field (Brunner et al. 2010; Fukuoka et al. 2015a; Koller et al. 2018). Importantly, the availability of different allelic forms is of interest for a geographic-based deployment of *R* gene diversity to match the pathogen's virulence profile. Moreover, some of these allele-mining studies have unveiled new allelic variants with a unique, broader spectrum of resistance (Das et al. 2012; Devanna et al. 2014; Fukuoka et al. 2015b). Secondly, PGR have acted as reservoirs of genuinely new disease resistance genes that were left behind during domestication and modern breeding: for example, the rice *Xa21* (Song et al. 1995) or the wheat *Yr36* genes (Huang et al. 2016) conferring resistance to bacterial leaf blight and stripe rust, respectively. Although the contributions of PGR to resistance breeding have been already relevant as exemplified by the above-mentioned cases, there is much more potential. Most breeders only reluctantly use non-adapted, old genetic material and an important challenge of the future will be to overcome the problems that are caused by classical introgression of such genetic resources.

However, a combination of the latest advances in genomics, next-generation sequencing (NGS) and HTGT technologies with population genomics has the potential to unveil the vast and untapped resistance genes hold in PGR populations to ultimately improve crop resistance. In the following, we

suggest strategies toward identification of new resistance sources using PGR collections.

GWAS-based isolation of disease resistance in PGR collections

Identification of resistance genes or quantitative trait loci (QTLs) is supported by genome-wide association studies (GWAS). GWAS explore historical recombination events accumulated over multiple generations in unrelated individuals, where all alleles for a trait of interest, with major and minor effects, are expected to be represented. This contrasts with the low genetic diversity of bi-parental mapping populations (Yan et al. 2011). Until very recently, there were two major difficulties when working with PGR collections. On the one hand, the scarcity of genetic makers made it difficult to introgress resistance genes into elite varieties due to linkage drag. On the other hand, due to the same problem derived from the lack of markers, much of the genetic diversity in PGR collections has not been explored. Both difficulties can be overcome with NGS and HTGT technologies. Technological progress and plummeting costs of NGS services allow the whole-genome sequencing of hundreds (or thousands) of accessions in plant species with small genomes like rice (The 3000 Rice Genomes Project 2014). With multiple genome sequences fully annotated, GWAS studies are currently used in mining resistance to different diseases affecting rice, uncovering multiple new allelic variants and resistance genes that are serving to broaden the diversity of resistance of commercial varieties (Raboin et al. 2016 and references therein).

However, for species with larger and more complex genomes such as wheat, barley or rye, whole-genome sequencing of thousands of accessions is still neither possible nor practical. Consequently, different reduced-representation sequencing technologies were developed for genotyping large PGR collections. For example, array-based SNP platforms allow a cost-effective and high-resolution genome-wide assessment of the genome diversity of PGR collections of barley (Bayer et al. 2017), rice (Chen et al. 2014; McCouch et al. 2016), wheat (Wang et al. 2014b; Winfield et al. 2016; Allen et al. 2017) and rye (Bauer et al. 2017). All these SNP-based arrays have benefited from high-quality whole-genome reference sequences of wheat (IWGSC 2018), barley (Mascher et al. 2017) and rice (International Rice Genome Sequencing Project 2005) to assign accurate physical positions to the markers. This is of special relevance to efficiently isolate disease resistance genes following map-based cloning or GWAS analysis approaches by facilitating the anchoring of molecular markers to small physical intervals pointing out directly a small set of candidates genes (Keller et al. 2018; Togninalli et al. 2018). In the near future, genomic information derived from multiple reference genomes can be expected in cultivated wheat, barley and their wild relatives. This information is highly useful both for the identification of candidate resistance genes by GWAS or through means of map-based cloning (Box 1).

Box 1: Genomics-assisted identification of resistance genes—the relevance of wheat and barley pangenomes

A single reference genome cannot capture the full genetic variability of resistance genes present in a species. Different genotypes show substantial genetic diversity due to structural variations in the form of copy number variants (CNVs) and presence/absence variants (PAVs) (Saxena et al. 2014). Therefore, the likelihood of finding a specific resistance gene in a single reference genome is low. For example, Chinese Spring (CS), the cultivar used to establish the reference sequence of bread wheat, has not been widely used in breeding due to its susceptibility to biotic and abiotic stresses (Sears and Miller 1985). Moreover, a recent chromosome-scale comparative analysis between chromosomes 2D of CS and the wheat genotype "*CH Campala Lr22a*", which carries the adult plant leaf rust resistance gene *Lr22a*, revealed large structural variations and four haploblocks with significantly increased single nucleotide polymorphism (SNPs). Three of those haploblocks showed CNV for NLR genes (Thind et al. 2018). This type of studies is of utmost relevance because SNPs and SVs are major contributors to phenotypic variation (Saxena et al. 2014).

Therefore, it would be desirable to have a complete genomic composition of a species, the so-called pangenome. Accordingly, the SHAPE project is laying the foundation stone of the barley pangenome with de novo whole-genome shotgun sequencing of two haplotypes profoundly distant at a genomic level from Morex, the cultivar used for the barley reference genome (SHAPE 2018). Likewise, a global wheat partnership is on the road toward the first wheat pangenome by sequencing ten wheat genomes from different origins around the world (Wheat Initiative 2018, http://www.10wheatgenomes.com/). Moreover, highly continuous genome assemblies for the wheat diploid donors of the A genome (*T. urartu*) (Ling et al. 2018) and D genome (*Ae. tauschii*) (Luo et al. 2017) and its allotetraploid progenitor, wild emmer (*T. turgidum* ssp. *dicoccoides*) (Avni et al. 2017) have been recently generated. These genomic resources will open up new avenues for implementing genomics-assisted resistance breeding in different ways (Bevan et al. 2017) (Fig. 1). Firstly, a pangenome will reveal genomic diversity between genotypes and allow the identification of novel alleles and genes not present in single reference genomes. Secondly, the incorporation of additional reference sequences will improve the SNP calling between multiples genotypes that until now have relied mainly on single reference genomes. Therefore, SNP-based arrays or exome capture designs will be implemented simplifying map- or GWAS-based isolation of genes by anchoring markers to smaller physical interval

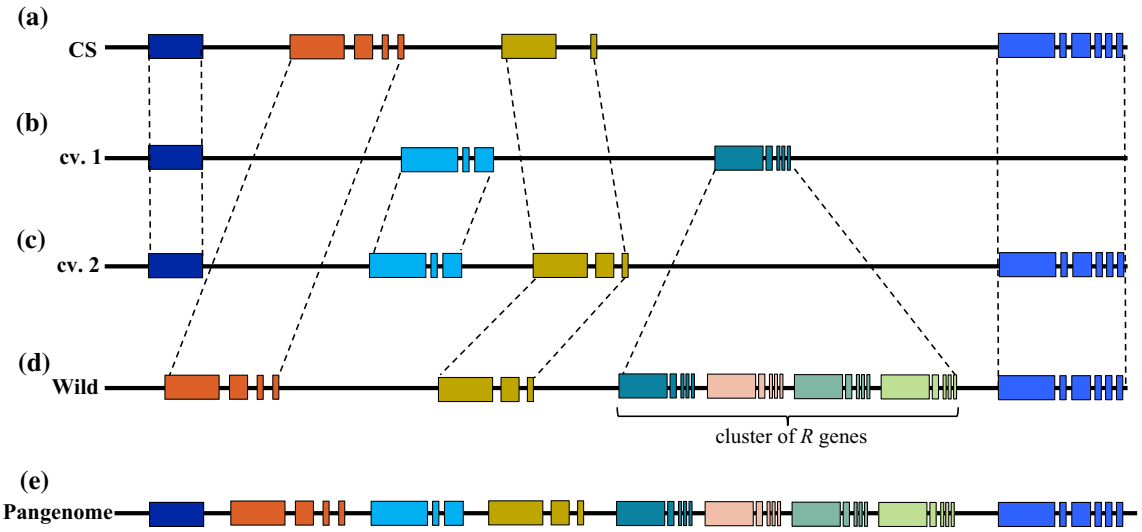


Fig. 1 Diagram of the wheat pangenome. **a** An example of a genomic region in Chinese Spring (CS) that consists of four *R* genes, the gold colored one is a pseudogene. **b** and **c** Two genomic regions in two elite cultivars. The incorporation of additional high-quality reference genomes results in the discovery of new resistance genes (light blue) absent in CS, or the complete cds of others (gold). **d** Genomic region of a wild relative displaying shared *R* genes with some of the elite varieties (orange, gold and dark blue) and a cluster of new *R* genes. **e** Resulting pangenome after the integration of genomic annotation from different elite varieties and wild relatives (color figure online)

targets or discovering rare alleles (Zhao et al. 2018). Thirdly, a pangenome formed by a given domesticated crop and its wild relatives provides a unique genomic structure to which all known variations can be anchored. This reduces the risk of missing out *R* genes present in wild relatives but absent in domesticated forms. Moreover, pangenomes including wild relatives will allow the identification of orthologues, an aspect of particular relevance in resistance breeding where resistance gene suppression of wild relatives-derived genes by their orthologues present in domesticated forms is a common phenomenon (e.g., *Pm8* rye-derived gene is suppressed by its wheat orthologue *Pm3CS* (Hurni et al. 2014). There, it was shown that the putative suppressor action of these orthologues can be tested in the *N. benthamiana* system. This might be generally true and suppressors could be eliminated by genome editing if necessary. Finally, thanks to bioinformatic-driven advances in NLR annotation, hundreds of NLR-encoding genes are predicted in cereal genomes (Steuernagel et al. 2018) serving as information on potential resistance genes, which can greatly assist the functional validation of candidates genes resulting from map- or GWAS-based approaches. Therefore, high-quality cereal genome sequences have enormous value and potential for gene cloning, and, a rapidly increasing number of molecularly isolated resistance genes can be expected.

An alternative genotyping approach to SNP arrays is exome capture (King et al. 2015), a genome complexity reduction strategy focused on sequencing the exome, which has allowed the discovery of markers in cultivated and wild relatives of barley (Wendler et al. 2014) and wheat (Allen et al. 2013). However, exome capture designs are biased by incorporating gene annotation of reference genomes. The sequencing of multiple reference genomes in the future will certainly assist in improved designs of exome capture arrays, but a small number of varieties cover only a small part of the genetic reservoir of resistance genes. Therefore, they are of limited use particularly for the highly diverse resistance genes. In contrast to exome capture arrays, genotyping-by-sequencing (GBS) (Elshire et al. 2011) represents an alternative genotyping approach that does not rely on a fixed set of SNPs and is reference-free. GBS involves targeted genome complexity reduction followed by restriction enzyme-based sequencing allowing marker discovery that is genome-wide and population specific. When GBS-based marker discovery is combined with association mapping, novel *R* genes/QTLs specific and unique to a selected population can be uncovered (Mgonja et al. 2017). GBS-based tagging of genomic regions harboring resistance genes in PGR collections is of particular importance because it would enable the discovery of resistance genes absent in reference genomes. SNP-based arrays or exome capture designs relying on reference genomes will miss out PGR-specific resistance genes. This makes GBS an excellent de novo marker platform for genomics-assisted breeding.

PGR collections for gene identification are most useful if they represent a maximal biological diversity of the trait of interest and there are efficient, high-quality phenotyping methods available. The overwhelming number of GR makes it virtually impossible to genotype all accessions. Therefore, efficient criteria to define useful genetic variation for

resistance breeding are needed. In this regard, "Focused Identification of Germplasm Strategy" (FIGS) can act as a proxy to select PGR with potential resistance genes (Mackay and Street 2004). FIGS assumes that adaptive traits can be linked to eco-geographic parameters, and, therefore, PGR from agro-ecological regions with disease-conductive conditions would represent reservoirs of resistant genes to diseases of those regions. Using FIGS, sources of resistance to barley net blotch (Endresen et al. 2012), rice blast (Vasudevan et al. 2014) or wheat powdery mildew (Kaur et al. 2008; Bhullar et al. 2009) have been found. FIGS might be further complemented by GS. Using a training population (a fraction of the whole PGR collection) for which both phenotypic and genotypic data are available, GEBVs are calculated following different GS models. The further selection of genotypes supposed to have beneficial alleles within the PGR collection are selected based on their GEBVs. GS has proven to facilitate the selection of superior accessions from big PGR collections in soybean (de Azevedo et al. 2017), maize (Pace et al. 2015) or in wheat for adult plant resistance to stripe rust (Meuwissen et al. 2001).

On the other hand, tremendous advances in genomics have shifted the research bottleneck in plant breeding from genotyping to phenotyping (Furbank and Tester 2011), which prevents us from translating genomic variants into desired resistance phenotypes (Araus et al. 2018). Therefore, there is an urgent need to develop phenotyping tools that a) increase the throughput of resistance screening under controlled and/or field conditions and b) reliably identify the genetic variants underlying phenotypes (Mahlein 2016). Fortunately, phenomics has progressed rapidly in recent years developing field-based, high-resolution and high-throughput sensor-based phenotyping tools (Simko et al. 2017; Shakoor et al. 2017) that deliver an improved, reproducible and accurate disease phenotyping at large scale. The future improvement of these techniques and their use in evaluating PGR collections for disease resistance would allow us to identify more efficiently genomic variants responsible for desired resistance phenotypes.

High-throughput isolation of gene family-specific resistance genes: fishing out NLRs

NLRs share distinct protein motifs that guide the design of specific probes for NLR-encoding sequences (Jupe et al. 2013), which can be used for gene isolation based on exome capture (Arora et al. 2018). Wild relatives are reservoirs of novel NLR genes, exhibiting extensive diversity (Jones et al. 2016). In a recent study, Arora et al. (2018) performed association genetics with NLR gene enrichment sequencing (AgRenSeq) in a panel of *Ae. tauschii* (donor of D genome of bread wheat) accessions to exploit the naturally occurring variation of NLRs. The phenotypic evaluation assessing race-specific resistance against stem rust with just seven isolates allowed the rapid molecular identification of four genuinely new NLR in a cost-effective manner and bypassed the need to generate mutant or recombinant populations. Moreover, AgRenSeq can be applied to distant wild relatives of domesticated crops that often show sexual incompatibility. Finally, AgRenSeq is reference-free, which is particularly attractive for the isolation of resistance genes, as these exhibit extreme accessional diversity (Noël et al. 1999). AgRenSeq and similar approaches promise to greatly speed up the discovery of new functional NLR genes, which can be introgressed into elite varieties either through MAS based on gene-specific markers or transgenic approaches ("Resistance gene introgression" section). Finally, when the current, most pathogenic strains are used, AgRenSeq provides a tailor-made resistance breeding strategy counteracting pathogen's virulence profile.

Rapid approaches for resistance gene isolation in non-reference cultivars

Until very recently, most disease resistance genes have been identified through high-resolution mapping and positional cloning, a burdensome and lengthy procedure taking several years. However, the combination of recent advances in NGS, bioinformatics and genome complexity reduction technologies resulted in several very rapid and efficient gene isolation approaches in cereals (reviewed in Periyannan 2018). A gene map-based approach named TACCA (targeted chromosome-based cloning via long-range assembly), based on high-quality sequences of flow-sorted chromosome carrying the resistance gene, identifies resistance genes using molecular marker information and ethyl methanesulfonate (EMS) mutants (Thind et al. 2017). Other approaches have moved away from map-based cloning and focused on mutagenesis and sequencing of a portion of the genome/transcriptome to identify resistance genes through mutational mapping [MutMap, (Abe et al. 2012)], mutant chromosome sequencing [MutChromSeq, (Sánchez-Martín et al. 2016)] or gene enrichment and sequencing [MutRenSeq, (Steuernagel et al. 2016)]. With these gene isolation techniques, it is now possible to isolate quickly each of the hundreds of known disease resistance genes described in major crops. Therefore, it is timely to isolate them for breeding applications. Besides, the research community has developed over many years a large series of NILs carrying *R* genes. They represent excellent material for the application of some of the above-mentioned gene isolation approaches.

In the two previous sections, we have described how to isolate *R* genes quickly. However, identifying candidate genes very rapidly does not make functional validation easier. Given the pace at which candidate genes can now be discovered, high-throughput functional genomic approaches are

urgently needed to determine if genetic variants are indeed functional in resistance (Box 2).

Box 2: Scaling up functional genomics—the relevance of improved and new functional genomics approaches

Transgenesis, the primordial functional validation approach used so far, is time-consuming and restricted to a narrow set of transformable genotypes. Moreover, transgene insertion and expression are uncontrolled and pleiotropic effects on plant growth and development may occur. Some of these drawbacks can now be overcome with improved transformation protocols or precise DNA insertion facilitated by genome editing technologies. Moreover, the latter can serve as a high-throughput functional genomic approach (Khatodia et al. 2016 and references therein). Nevertheless, novel and faster, complementary functional genomics approaches are urgently needed.

In this regard, it would be worth exploring possibilities offered by "effectoromics," a powerful tool to identify host resistance genes and matching pathogenic avirulence genes in plant-oomycetes pathosystems based on transient expression *Agrobacterium*-based functional assays (Vleeshouwers and Oliver 2015). Although still nascent in cereal-fungi pathosystems, we believe that this approach can greatly assist in the functional validation of candidate *R* genes. For example, the validation of the set of *R* candidates derived from an AgRenSeq study could be supported by the agro-co-infiltration with core pathogenic effectors obtained from field samples in *Nicotiana benthamiana* checking for *R* gene-specific hypersensitive response. Consideration, however, needs to be given to genetic interactions exhibited by some *R* genes (Resistance gene deployment and management: a view to the future), which can make *R* validation through effectoromics challenging. Besides, effectoromics assumes a direct interaction between the R-AVR pair of proteins, which is not always the case. Therefore, independent and complementary functional assays are required to confirm the resistance action of candidate genes, like Virus Induced Gene Silencing (VIGS) (Lee et al. 2012) or reverse genetic approaches like TILLING (Targeting Induced Local Lesions IN Genomes) (Krasileva et al. 2017).

Isolation of genes underlying quantitative disease resistance

Very few QDR loci have been cloned to date, including two wheat leaf rust resistance genes: *Lr34* (Krattinger et al. 2009) and *Lr67* (Moore et al. 2015b); a wheat yellow rust resistance gene: *Yr36* (Fu et al. 2009); and a recessive rice blast resistance gene *pi21* (Fukuoka et al. 2009). The main limitation identifying genes underlying QDR resistance stems from the difficulty of obtaining reliable genotype–phenotype associations. QDR resistance is controlled by many genetic loci, which individually have small effects, thereby hampering an appropriate disease scoring. The question is "how can we adequately select genes—in particular, those with small effects- underlying QDR?" Choice of the population, reproducible and accurate phenotyping and identification of mutants are the critical elements in ensuring a proper selection of genetic determinants of QDR.

Population choice: nested association mapping (NAM)

The use of recombinant inbred lines based on multiparent cross-designs, such as nested association mapping (NAM) populations, has been proposed for fine-scale mapping and marker-trait associations of complex traits by combining the advantages of association mapping (high mapping resolution) and linkage mapping (power of QTL detection) (Yu et al. 2008; Buckler et al. 2009). A NAM population encompasses a wide range of genetic diversity derived from multiple recombinant inbred line (RIL) families connected by a common cultivar that acts as a recurrent parent. The genetic diversity is generated by a) the shuffling of parental alleles over generations through segregation and genetic recombination, and (2) the historical recombination of haplotypes present in the donor parents. The resulting genetic diversity encapsulates all allele variants whose frequencies are balanced and with rare variants enriched, thereby increasing the odds of discovering rare alleles. Moreover, it has been reported that the genetic background may influence QTL effects due to epistasis and pleiotropy (Holland 2007; Mackay et al. 2009). NAM populations, as multi parental populations, are able to unravel such effects that would go unnoticed in simple genotypes such as NILs. First promising steps in the use of NAM populations for the genetic dissection of QDR are being taken for stem rust resistance in wheat (Bajgain et al. 2016) or net blotch resistance in barley (Vatter et al. 2017). Decades of fieldwork in nurseries gives us access to rich phenotypic data on cultivars proven to have durable and stable resistance over long periods across large areas without resistance breakdown. These cultivars must now be identified and used as recurrent parents in the development of NAM populations. The advance of HTGT technologies facilitates genome-wide genotyping of NAM populations. Having said that, new phenotyping approaches are needed to achieve the genetic dissection of QDR.

Accurate, reliable and reproducible phenotyping

Visual scoring is admittedly subjective and error-prone (Poland and Nelson 2011). While this might not be critical when evaluating *R* gene-mediated resistance, in the case of QDR an accurate and reproducible evaluation is essential. Sophisticated technologies based on hyperspectral and thermal imagining (Mutka and Bart 2014), chlorophyll fluorescence imagining (Rousseau et al. 2013) or microphenomics

(Douchkov et al. 2013) can greatly assist identifying genetic variants controlling QDR as these techniques quantitatively measure disease incidence, as recently demonstrated in the Septoria tritici blotch–wheat pathosystem (Karisto et al. 2018). Moreover, the environment can significantly influence QTL expression (Gutiérrez et al. 2015), which requires a valuation at contrasting locations. Therefore, we suggest that future QDR studies would employ regionally adapted varieties with proven durable and stable resistance as the recurrent parent of NAM populations, which would be evaluated at multiple sites using non-invasive and automated phenotyping platforms that can quantitatively assess resistance under near-field conditions during disease development (Thomas et al. 2018).

The role of mutants in the genetic dissection of QDR

EMS-derived mutants have been proven to support the identification of QDR loci. For example, the multipathogen "pleiotropic" resistance wheat QTLs, *Lr34/Yr18/Sr57/Pm38* (Krattinger et al. 2009) and *Lr67/Yr46/Sr55/Pm46* (Moore et al. 2015a) were isolated by positional cloning, assisted by EMS-induced mutants. This was possible because of their strong phenotypes. Therefore, for those major QTLs for which mutants can be identified, gene isolation techniques such as MutChromSeq (Sánchez-Martín et al. 2016) certainly can speed up the QTL isolation process. In the case of minor QTLs, although the identification of EMS mutants is unlikely, we believe that mutants can still play a substantial role. Nested genome-wide association (GWA) mapping has finely mapped regions associated with QDR in Arabidopsis (Huard-Chauveau et al. 2013; Debieu et al. 2016) and in wheat (Bajgain et al. 2016), resulting in a small number of candidates genes. Further detailed phenotypic evaluation of such limited numbers of candidates genes can then be done with mutants generated from resistant parent-derived TILLING populations (Hurni et al. 2015) or insertional mutants (T-DNA) (Debieu et al. 2016). Therefore, the development of EMS-derived and TILLING mutants in genotypes of interest seems to be promising to assist in the validation of major- and minor-effect QTLs, respectively.

The emerging importance of pathogenomics in resistance breeding

Classical work on the diversity of wheat fungal pathogen populations has characterized field isolates based on their virulence on near-isogenic lines (NILs) carrying known *R* genes. This approach results in a limited understanding of pathogen diversity as it only describes virulence or avirulence to a few, known genes Thus, NIL-based characterization only provides a partial understanding of the pathogen's biology and population structure. Nowadays, NGS and HTGT technologies offer an unbiased characterization of pathogen populations, both at the organismal and molecular levels. Genomic and transcriptomic data from field samples, so-called *field pathogenomics*, can rapidly define the population structure and genetic diversity of pathogens (Möller and Stukenbrock 2017), which, if spatially and temporally monitored, can predict emerging epidemics by uncovering diversity changes and population structure shifts (Hubbard et al. 2015) and pathogen surveillance activities. Moreover, this data allows to rapidly define lineage-specific repertoires of effectors (Zhong et al. 2018). When compared with each other, a core of effectors can be defined (Dangl et al. 2013). Together with the increasing number of effectors characterized at the molecular level allowing the design of specific molecular markers (reviewed in Bourras et al. 2018), this pathogen-derived information opens up new avenues to improve resistance through so-called effector-assisted breeding. For example, it might guide identification of *R* genes, redirecting efforts toward genes matching the pathogen's virulence pattern ("Resistance gene deployment and management: a view to the future" section), or predict the durability of to-be-deployed *R* genes (Vera Cruz et al. 2000). Furthermore, resistance breeding would benefit from releasing *R* genes that recognize the most conserved effectors among pathogenic strains. Genomic-level studies can reveal pathogen evolution processes that result in newly emerged pathogens like the wheat blast pathogen (Inoue et al. 2017) or novel powdery mildew forms able to infect rye–wheat amphiploid species (Menardo et al. 2016). This type of information must be considered for successful resistance introgression. Thus, pathogen-informed strategies will play an increasing role in resistance breeding in the future. After the long decline of the once popular virulence studies in fungal populations, the molecular understanding of pathogens is currently contributing to a revival of integration of pathogen information to the breeding process. Although *R* gene-based resistance breeding will mostly profit from effector-assisted breeding, pathogenomics will possibly also develop into an important tool for the work with QTL for resistance. Recently, transcriptome analysis showed that mildew and rust pathogens growing on host plants carrying the broad-spectrum resistance QTL *Lr34* from wheat do not show alterations in gene expression (Sucher et al. 2018). Thus, there is no physiological response of the pathogens to the presence of this resistance gene, possibly explaining why pathogens have not adapted to *Lr34* despite the intensive use of this gene in last more than 100 years. It is tempting to speculate that this absence of transcriptional response could be the hallmark of durable resistance QTL, a hypothesis that remains to be tested in NILs containing known QTL for resistance.

Resistance gene introgression

With the gene isolation techniques mentioned in "Rapid approaches for resistance gene isolation in non-reference cultivars" section, it is now possible to isolate quickly each of the hundreds genetically described disease resistance genes in barley, rice and wheat. It is time to set the goal to isolate all of these genes with potential value for resistance breeding and to increase crop disease resistance within elite varieties. The question that arises is "how can we incorporate into elite varieties all those genes?" The answer largely depends on the species source of the resistance gene.

Introgression from sexually compatible relatives

If the donor parent belongs to the primary gene pool or the loci of interest are present in a homologous chromosome of a species belonging to the secondary gene pool, resistance introgression is moderately feasible via marker-assisted backcrossing (MABC): sexual crossing, backcrossing and selection. The isolation of the gene of interest following one of the approaches explained in "Genebanks: treasures of genetic diversity waiting to improve resistance breeding" through "Isolation of genes underlying quantitative disease resistance" sections provides the "perfect marker," a gene/allele-specific marker that greatly assists the selection of the loci of interest while recovering the recurrent parent genome almost entirely in a few backcrossing generations. Besides, MABC can be underpinned by novel breeding-based approaches to speed up resistance introgression by shortening plant generation times. For instance, Ruengphayak et al. (2015) proposed a pseudo-backcrossing design for rapid introgression of traits in rice. Other approaches combine embryo culture with specific growth conditions to generate multiple generations of barley and wheat per annum (Zheng et al. 2013; Hickey et al. 2017). Finally, Watson et al. (2018) using supplemental lighting under controlled conditions prominently accelerated the traditional single seed descent approach to generate multiple generations per year, allowing at the same time phenotyping on-the-go, a clear advantage compared to double haploid technology. This approach, called *speed breeding*, holds great promise for rapid resistance introgression into domesticated crops from sexually compatible relatives in the context of "traditional" resistance breeding, speeding up the development of disease-resistant varieties tremendously.

Introgression from distant relatives

If the donor species belongs to the tertiary gene pool or the locus of interest is present in a non-homologous chromosome from a species from the secondary gene pool, resistance introgression is much more challenging. If hybrids are possible, interspecific hybridization can be performed by sexual hybridization supported by cytological techniques. Alternatively, in the presence of sexual incompatibility, chromosome-engineering approaches mediated by asymmetric somatic hybridization are required. The resulting introgression lines (ILs) are pre-breeding lines with introgressed segments of highly variable size harboring the gene of interest. They can then be backcrossed to recover the recurrent parent genome. Although widely recognized as rich sources of resistance (Hajjar and Hodgkin 2007), ILs barely have been involved in the development of elite varieties due to the lack of appropriate high-throughput technologies to screen, identify and select small introgressions with the resistance gene (to eliminate linkage drag) and reduced interspecific recombination frequencies in the introgressed regions (Kilian et al. 2011). Nowadays, the detection efficiency of alien introgressions, their characterization in term of size and their tracking through breeding programs is greatly assisted NGS technologies. The availability of SNP-based arrays derived from hexaploid wheat and its secondary and tertiary gene pool (Winfield et al. 2016) allows to track introgressions precisely through the process of backcrossing and selfing, while selecting the smallest introgression in interspecific wheat/wild relatives F1 hybrids (King et al. 2017). Likewise, GBS and exome capture designs derived from species of the secondary gene pool (Wendler et al. 2014) enable a precise genetic characterization of barley/wild relative introgression lines (Wendler et al. 2015). These two examples highlight the relevance and practical use in resistance breeding of extending HTGH and NGS technologies to the secondary and tertiary gene pools of domesticated crops allowing more efficient use of ILs in resistance breeding by reducing the size of the fragments and then reduce linkage drag. However, one cannot ignore the fact that deleterious genes will be introgressed along with the gene of interest even when the alien introgression are selected for small size. In such cases, resistance introgression needs to be done by transgenesis.

Transgenesis-based introgression of resistance

A faster way to introgress resistance circumventing sexual incompatibilities, linkage drag and genes linked in repulsion hampering their selection (e.g., *Sr31*, *Sr33*, *Sr50* (Ellis et al. 2014) is through genetic transformation of elite varieties with resistance genes (Rodriguez-Moreno et al. 2017). Transgenesis-based resistance has been successfully used in rice (Kumari et al. 2017) or wheat (Brunner et al. 2011, 2012b; Koller et al. 2018) via *Agrobacterium*-mediated or particle bombardment methods. Interestingly, the overexpression of the transgene might lead to resistance in the field even though the resistance gene has been overcome in

natural cultivars (Koller et al. 2018). Transgenesis, unable to control where the transgene is inserted, is not free of silencing by the genetic background surrounding the insertion site (Matzke and Matzke 1998). Consequently, technologies that allow a controlled insertion of the transgene, such as CRISPR/Cas9 (reviewed in Khatodia et al. 2016), when combined with gene cassettes (explained below), would be a very promising approach in resistance breeding.

Clusters of different *R* genes cloned into the same vector and jointly transformed into a preferential variety, so-called genes cassettes, have been proposed to overcome the limitations mentioned above (Wulff and Moscou 2014). Moreover, the genetic basis of *R* genes used in gene cassettes can be broadened by different means. Firstly, naturally occurring allelic variants with extended or different resistance spectra can replace alleles with reduced resistance specificity and secondly through engineering new *R*-mediated resistance specificities (Zhang and Coaker 2017; Cesari 2018; De la Concepcion et al. 2018). There are the first successful reports to engineering new resistance specificities based on information derived from allele-mining studies. For example, in the work of Stirnweis et al. (2014), the substitution of two amino acids in Pm3f resulted in a broader resistance specificity, very similar to the one conferred by the Pm3a protein. These results highlight the relevance of allele mining and its practical use in resistance breeding.

Initially conceived as a package of *R* genes, mainly NLR-encoding genes, these gene cassettes can be now complemented with the inclusion of genes governing non-host resistance and QDR, and thus enhancing disease resistance. For instance, the rice PRR XA21 confers resistance bacterial blight of rice by recognizing a conserved sulfated peptide from *Xanthomonas oryzae* pv. *oryzae* (Pruitt et al. 2015). Moreover, including QDR genes that are affecting different stages of the pathogen infection process is particularly attractive. For example, Li et al. (2001) proved that pyramiding genes with a different mode of action on the pathogen could extend the durability of pyramid-based resistance. This kind of gene pyramids would represent a nearly insurmountable barrier for the pathogens but requires a very detailed physiological understanding of the action of each individual QDR.

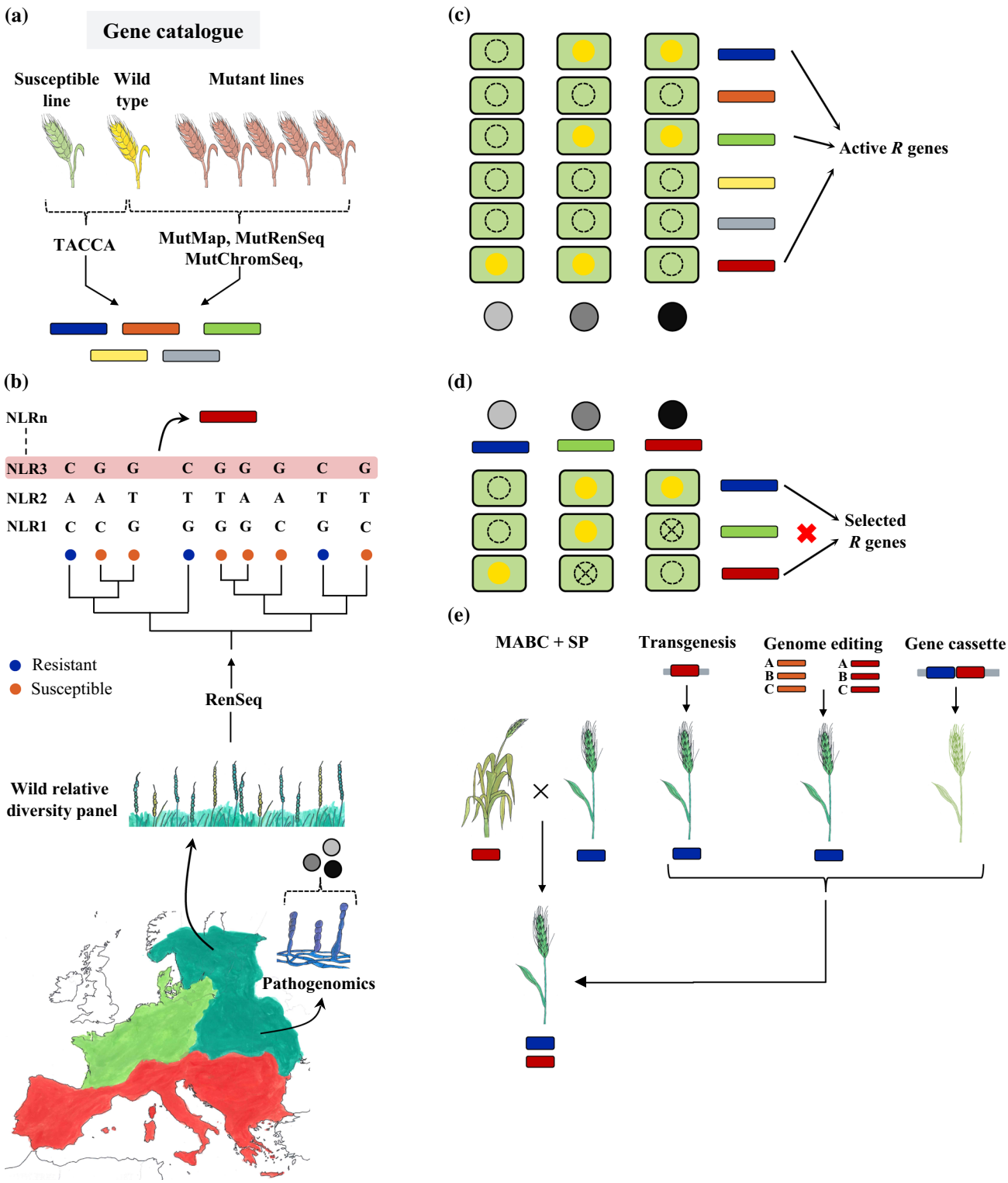
A further much-discussed approach, not yet adequately tested, is host-induced gene silencing (HIGS) of small interfering RNAs that may silence essential genes in the pathogen (reviewed in Nunes and Dean 2012). If promising results obtained to date in transient gene expression assays were further confirmed in transgenic plants, we would get confidence that HIGS is a viable technology for resistance breeding.

Nevertheless, transgenesis and genome editing approaches are hampered by relatively low transformation efficiencies and limited to a narrow range of transformable varieties, especially in wheat and barley. Despite recent improvement in transformation protocols and thereby widening the genotype range for transgenics (Wang et al. 2017), their practical use in resistance breeding is still very far from reaching a massive scale level. Besides, legal barriers resulting from the negative public perception of transgenic plants in certain areas, especially in Europe, discourage the use of these approaches by many breeders. Consequently, we advocate for "a more realistic and implementable" resistance breeding strategy based on a multiresistance gene by pyramiding as described below. Nevertheless, we consider it to be important to emphasize in public discussions related to future changes in regulatory procedures that transgenic approaches have an enormous potential to provide strong and efficient resistance (Wulff and Dhugga 2018; Koller et al. 2018), allowing to reduce fungicide use, another important goal of our societies.

Resistance gene deployment and management: a view to the future

Rotations in space and time of multilines or mixtures of agronomically very similar varieties differing in resistance genes (Mundt 2002) prevent pathogen spread by increasing host variety and barrier effects (Pink 2002). This strategy, adopted in barley (Wolfe 1992) and rice agro-systems (Zhu et al. 2000), has faced deployment difficulties due to the lack of uniformity among varieties, hampering its use in other agro-systems, such as wheat (Pink 2002). Nevertheless, transgenic multilines have proven to be effective to counter wheat powdery mildew (Brunner et al. 2012b). However, given the operational difficulties at farming level, we advocate using regionally adapted cultivars with pyramided resistance genes.

The combination of *R* genes into a single cultivar—gene pyramiding—(Hsam and Zeller 2002; McDonald and Linde 2002), has been used to lengthen the durability of the *R*-mediated resistance under the pretext that pathogens would require changes in multiples *Avr* genes to bypass host recognition (Hsam and Zeller 2002; McDonald and Linde 2002). Many reports have proven the value of *R* pyramiding to counter, for example, wheat powdery mildew (Liu et al. 2000) or rice blast (Hittalmani et al. 2000). Although close markers to the gene of interest have been proven useful in MABC schemes, we have advocated the isolation of *R* genes due to two reasons. First, gene/allele-specific markers are highly diagnostic and can be used in any genetic background (Miedaner and Korzun 2012). Second, the isolation of genes might allow checking for eventual compatibility and suppression effects. Some *R* genes act additively [e.g., the wheat stripe rust genes *Sr24* and *Sr26* (Roelfs 1988), or the *Lr10*-mediated resistance to leaf rust in wheat (Loutre et al. 2009)]. Other introgressed genes are suppressed by their



homologues, as the *Pm8* rye-derived gene is by its wheat homologue *Pm3* (Hurni et al. 2014). Finally, *R* genes can interact with APR genes like the wheat *Lr34* enhances the effectiveness of some *R* genes (German and Kolmer 1992; Vanegas et al. 2008). These aspects represent limiting factors in *R* pyramidization and should be identified before starting the backcrossing process (Sánchez-Martin et al. 2018). In this regard, transient assays can assist in the rapid detection of suppressive interactions between resistance genes (e.g., the *Pm3–Pm8* case).

◂**Fig. 2** Diagram of a possible resistance breeding strategy for the geographic region colored in turquoise. **a** Cloning of described resistance genes using approaches described in "Rapid approaches for resistance gene isolation in non-reference cultivars" section. **b** AgRenSeq on a wild relative diversity panel and field pathogenomics ("High-throughput isolation of gene family-specific resistance genes: fishing out NLRs" section). **c** Co-infiltration in *N. benthamiana* of resistance genes (colored bars) and core pathogenic effectors (gray colored circles). Specific resistance responses represent candidate *R-Avr* pairs, depicted as yellow circles in leaves (green squares). **d** *N. benthamiana*-based co-infiltration assay checking for incompatibilities between different *R* genes when co-infiltrated with *Avr* effectors. The co-infiltration of the red and green *R* genes does not result in HR, due to, for example, a suppression phenomenon: the wild-derived red gene is suppressed by its wheat orthologue (light green), similar to the *Pm3–Pm8* case. Consequently, red and blue *R* genes are the selected genes to be introgressed into an elite variety. **e** Introgression resistance strategies, considering a wild relative with the red *R* gene and an elite variety with the blue *R* gene following a marker-assisted backcrossing approach (MABC) supplemented with speed breeding (SP), trangenesis or genome editing approaches. Finally, the figure considers the case of introgression by means of a gene cassette strategy into another elite variety (light green). The strategy would be implemented across time, selecting *R* genes to be introgressed based on the pathogen-derived information. Finally, the strategy would be implemented in regions colored in red and in green light in a similar way. Note that the colored geographic regions correspond to hypothetical scenarios where it is assumed the presence of the same pathogenic race (color figure online)

The overarching prerequisite for the success of any breeding strategy for durable resistance depends on deployment strategies that exert less selective pressures on the pathogen (Burdon et al. 2016). To do so, we propose the implementation of resistance breeding strategies that have two main features (Fig. 2). Firstly, it has a multigene nature, including *R* and QDR genes (cloned as described in "Genebanks: treasures of genetic diversity waiting to improve resistance breeding" through "Isolation of genes underlying quantitative disease resistance" sections) that desirably act in different aspects of the pathogen life cycle. The introgression of the resistance is achieved following a MABC strategy under *speed breeding* conditions as presented in "Introgression from sexually compatible relatives" and "Introgression from distant relatives" sections. Alternatively, where legally possible and commercial varieties are amenable to transformation, the gene cassette strategy could be implemented. This multigene resistance, guided by pathogen-derived information, is deployed following a mosaic design at the local or regional level to match pathogen's virulence profile. By doing so, breeders will broaden the genetic diversity at the gene (different resistance components) and plant level (different hosts), thereby mimicking as much as possible the genetic diversity present in PGR populations in natural environments, and then reducing evolutionary pressure on pathogen populations. Secondly, the resistance is deployed dynamically over time, incorporating new resistance components to counter new pathogenic strains. Given the declining sequencing costs, genomics-informed, real-time, global pathogen surveillance protocols will be commonplace soon, enabling the monitoring of allelic frequencies of *Avr* genes and potential changes in pathogen populations. All this will guide rational resistance deployment strategies matching current and predicted pathogen's virulence at a regional level. If so, breeders will break up the adaptative landscape, and thus relieve the evolutionary pressure on pathogen populations to ultimately lengthen the durability of the resistance (McDonald and Stukenbrock 2016).

Unresolved questions and future challenges

Genome editing: the Trojan horse to introgress resistance

There is a growing interest to silence (modify or suppress) plant genes that act as "Trojan horses" to the plant resistance machinery, the susceptibility (*S*) genes: host targets manipulated by pathogen effectors that lead to the plant immune system disarmament (Pavan et al. 2010). By selecting against an *S* gene, an essential component for pathogen replication or effector target is eliminated and plants become recessively resistant. There are some rare, but very relevant and successful cases of loss-of-function *S* genes used in resistance breeding. For example, the well-known naturally occurring mutation of the *Mlo* gene in barley confers broad-spectrum resistance against the barley powdery mildew (Jorgensen 1992), or the *pi21* recessive mutation associated with durable resistance to rice blast (Fukuoka et al. 2009). With the advent of genome editing technologies able to manipulate precisely specific genomic sequences susceptibility genes can be "switched off" (Zaidi et al. 2018). One of these genome editing technologies, CRISPR/Cas9, excels above the rest since it allows simultaneous multisite editing (Cong et al. 2013), which is particularly attractive for polyploid species, such as wheat, allowing simultaneous targeting of the homoeologous gene copies in all the subgenomes. However, precautions should be taken in this regard, as multifunctionality and pleiotropic effects might limit the use of *S* genes in resistance breeding. For example, although *mlo* mutants confer resistance to the barley powdery mildew, the resistance against necrotrophic and hemibiotrophic pathogens is compromised (McGrann et al. 2014). Likewise, the disease-susceptibility gene *Xa13/Os8N3/OsSWEET11* conferring resistance to rice bacterial blight is required for reproductive development (Chu et al. 2006). Besides, genome editing is genotype specific. Therefore, the disruption of *S* genes would require a one-by-one evaluation of their agronomic viability.

Identification of non-canonical *R* genes: beyond NLRs

In most of the known gene-for-gene relationships NLRs recognize Avr effectors. However, the wheat *Stb6* gene encodes a conserved wall-associated receptor kinase (WAK)-like protein (Saintenac et al. 2018). It recognizes an apoplastic effector (Zhong et al. 2017) and suggests that resistance genes not encoding NLRs might play a critical and currently underestimated role in race-specific resistance. Furthermore, WAK genes have been found to play an important role in disease resistance in rice and maize (Hurni et al. 2015). Therefore, given the widespread presence of WAK genes in cereal genomes (Vogel et al. 2010; IWGSC 2018), it is of utmost importance to further study WAK genes as new players in race-specific resistance in cereals. One could consider the possibility to "capture" all WAK genes present in a PGR collection and test for resistance in PGR similarly to what has been done by Arora et al. (2018).

Summary points

- Genebanks form the basis for studies on the genetic diversity of resistance and provide the raw material for resistance breeding. Our success translating genomic variants into desired resistant phenotypes will largely depend on our capability to wisely select GRP collections by, for example, allele-mining tools such as FIGS. These populations can be now accurately genotyped and phenotyped.
- There is a wide range of rapid and accurate approaches for the isolation of major resistance genes. These approaches must be used to isolate all useful, genetically described resistance genes. Furthermore, new *R* and QDR genes need to be identified to further introgress them by MACB, genetic transformation or genome editing.
- Resistance breeding should be multigenic in nature. Its genetic components should be tested beforehand to avoid, for example, incompatibilities as exemplified by the *Pm3–Pm8* suppression case. If genes are cloned, transient expression assays like the *N. benthamiana* give rapid answers.
- *R* gene diversity is not limited to NLR-encoding genes, but encompasses other players, such as WAKs. The identification of all type of genetic components involved in resistance is of utmost importance to improve crop disease resistance.
- Transcriptomics has shown as useful tool for the genetic dissection of both *R* and QDR genes and for studying pathogen reaction as well. The effective incorporation of transcriptomics in resistance gene isolation will be decisive for the future isolation of many resistance components.
- Eliminating susceptibility genes by genome editing is conditional upon agronomic viability, which requires a one-by-one evaluation.
- The establishment of pangenomes will expedite resistance gene cloning. This requires large international collaborations.
- The isolation of the corresponding avirulence genes for each disease resistance gene will greatly help to get a better molecular understanding of disease resistance. The information derived will further our knowledge in *Avr/R* gene biology that could guide long-term durable resistance breeding strategies.
- The (re-)emerging research area of field pathogenomics will play a substantial role in resistance breeding. Constant spatial–temporal pathogen population surveillance programs for major crop diseases need to be implemented to study pathogen diversity and diversity and guide resistance deployment strategies as well.
- The development of robust phenotyping tools is urgently needed to close the current phenotyping bottleneck that prevents us from translating the vast and now accessible genetic information to desired resistant phenotypes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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