Navigating complexity to breed disease-resistant crops

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Abstract | Plant diseases are responsible for substantial crop losses each year and pose a threat to global food security and agricultural sustainability. Improving crop resistance to pathogens through breeding is an environmentally sound method for managing disease and minimizing these losses. However, it is challenging to breed varieties with resistance that is effective, stable and broad-spectrum. Recent advances in genetic and genomic technologies have contributed to a better understanding of the complexity of host–pathogen interactions and have identified some of the genes and mechanisms that underlie resistance. This new knowledge is benefiting crop improvement through better-informed breeding strategies that utilize diverse forms of resistance at different scales, from the genome of a single plant to the plant varieties deployed across a region.

Landraces
Traditional plant varieties that have been developed through informal (farmer-based) breeding.

Germplasm
Living material, such as seeds or tissues, from which new plants can be grown that is maintained for the purpose of preservation, breeding and other uses.

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An estimated 13% of global crop yields are lost to diseases annually[1,2]. The extent of these losses varies by crop and by region but is greatest in the tropics and subtropics where conditions favour disease development[1]. Although chemical control is an efficient method of disease management, overall crop losses have not declined over the past half century, while pesticide use has dramatically increased. Instead, pesticides have allowed farmers to intensify production systems without incurring greater losses[2]. Harnessing host resistance through crop breeding offers an effective and reliable alternative to pesticides[3] that can be combined with other management practices in integrated approaches. For example, disease-resistant crops perform better with timely planting and harvest and with crop diversification[4]. However, resistance breeding is challenging. Although plants have evolved a range of mechanisms for resisting disease, the dynamic and evolving nature of host–pathogen interactions means that virulent pathogen populations can arise and overcome formerly resistant crop varieties[4]. Resistance breeding is therefore an ongoing process, and resistance must be managed strategically. For this reason, resistance breeding programmes systematically test wild relatives, landraces and other germplasm to identify new genetic sources of resistance to important pests and pathogens (BOX 1).

While simple resistance (based on a single gene) can be effective in the short term, successful long-term resistance requires genetic complexity at multiple scales. In both the short term and the long term, effective disease resistance depends on phenomena that play out at the level of genes, genotypes and populations, and these factors must be considered throughout the resistance breeding process. When genes and genomic loci that confer disease resistance are identified, they can be assessed in terms of the strength of their effect, their race specificity and their potential contributions to durability. At the genotype level, the performance of resistance is influenced by the number of resistance genes and their specific combination in the host. In a breeding programme, the direct or indirect effects of resistance genes on other valued traits need to be taken into account; such traits include, among others, grain quality, adaptation to environmental conditions and yield. Finally, population-level effects on the durability of resistance and the spread of disease need to be considered.

Here, we review the ways in which resistance breeding programmes can benefit from increased understanding of the genes that confer host resistance to plant pathogens and from improvements in genetic technologies. We discuss how genomic approaches are helping to identify increasing numbers of genes, including those with small phenotypic effects; how the resulting insights into the mechanisms and trade-offs involved in plant defence can inform the design of new resistance genotypes; and how new genomic technologies can complement traditional resistance breeding to generate resistant varieties. We also discuss the importance of establishing genetically diverse host populations at the plot, farm and landscape levels for effective disease management.

Resistance types, genes and mechanisms

Qualitative and quantitative resistance. Resistance is typically recognized as being either qualitative or quantitative (FIG. 1). These terms are used to distinguish both

Box 1 | **Germplasm collections**

Breeding programmes must continually incorporate new forms of resistance to rapidly evolving pathogen populations. Breeding for resistance therefore requires a ready supply of resistance alleles that can be incorporated into crop varieties. This underscores the need for crop genetic resource conservation[141]. Germplasm collections collect, curate and characterize diverse germplasm that may include novel types of disease resistance. These collections are made available to breeders and potentially to farmers and others who are looking to regain or retain valued crop varieties. Genesys (https://www.genesys-pgr.org/welcome), an information portal for a global network of gene banks that provides information on stored seeds and other genetic resources, currently consists of over 400 institutes that collectively curate approximately 3.6 million accessions. Exploitation of this genetic diversity has its challenges. It is difficult to evaluate resistance in an environment in which the disease is not always present or in an environment to which the material is poorly adapted. The effects of specific resistance alleles may depend on genetic backgrounds[36,142]. The effects of minor quantitative resistance loci may be too small to detect reliably, particularly in the presence of resistance genes. However, genetic and genomic analysis of wild and rustic germplasm can circumvent some of these difficulties and provide insights that increase the utility of the genetic heritage of cultivated crops[143,144]. For example, molecular analysis can reveal the underlying genetic structure of germplasm collections to inform sampling, and sequence-based searches can reveal novel alleles at genes of interest.

the phenotypic expression of resistance and the type of inheritance typically associated with each[5]. Resistance genes (R-genes) underlying qualitative resistance tend to provide complete or near-complete resistance and are therefore also known as major genes. Studies of qualitative resistance have yielded a detailed understanding of pathogen recognition and response[6], as major genes for resistance typically (but not always) encode proteins involved in pathogen recognition. R-genes typically show dominant phenotypes, but recessive resistance genes also occur. Recessive resistance may be caused by loss-of-function variants of genes that confer susceptibility to disease (that is, dominant susceptibility genes (S-genes)[7–9]; BOX 2).

By contrast, quantitative disease resistance (QDR) shows an incomplete or partial phenotype and is controlled by multiple genes of small effect[5] (FIG. 1). Genes conditioning QDR are known as minor genes and map to quantitative trait loci (QTLs). Progeny of a cross between a line with strong QDR and one with weak QDR typically show a continuum of phenotypic variation. Research into QDR has characterized the genetic architecture of resistance in different pathosystems[10]. As for most quantitative traits, genetic dissection of QDR is challenging, and the relationship between phenotypes and molecular mechanisms is not as well understood as it is for qualitative resistance. The genes that condition QDR have only recently begun to be identified (TABLE 1 and Supplementary information S1 (table)). It should be noted that some of these genes have roles in pathogen recognition (more typically associated with qualitative resistance), demonstrating that genes resembling R-genes can have incomplete effects and be identified as QTLs in mapping studies[11]. Thus, although the concepts of qualitative and quantitative resistance often have been presented as a dichotomy, in reality, a continuum of scenarios can exist[11].

Studies of plant immunity in model systems such as *Arabidopsis thaliana*, tomato and rice have revealed a great deal about the mechanisms underlying disease resistance in plants[6]. There are two main mechanisms involved in the plant immune response: pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI; also known as basal resistance) and effector-triggered immunity (ETI). PTI is a broad-spectrum resistance that is triggered in response to conserved pathogen features (PAMPs)[6,12]. PAMPs are recognized at the plant cell surface via conserved pattern recognition receptors (PRRs), which are typically membrane-localized receptor-like kinases (RLKs)[13] or wall-associated kinases (WAKs)[14] (FIG. 2). PTI is thought to be an important factor in non-host resistance, the phenomenon whereby most plants are resistant to most microbial pathogens[15,16]. It can also contribute to quantitative resistance[17]. By contrast, ETI forms the basis of qualitative resistance.

Genes and mechanisms that confer qualitative resistance. ETI is activated when plant resistance proteins (R-proteins, encoded by R-genes) recognize their corresponding pathogenic effector protein[18]. R-proteins typically belong to one of several structural protein types that are encoded by nucleotide-binding domain leucine-rich repeat containing (NLR) genes, and most R-genes encode cytosolic NLR proteins[19]. However, as more R-genes are cloned, it is becoming apparent that they confer resistance by a range of different mechanisms; for example, some R-genes encode detoxification enzymes[20], while others encode WAKs[14]. ETI is often manifested as a hypersensitive response (HR): that is, rapid cell death localized at the point of pathogen penetration. While the HR can be effective in blocking disease caused by biotrophic pathogens, cell death can benefit necrotrophic pathogens. NLR proteins are thus not generally effective for defence against necrotrophs and have in fact been implicated in susceptibility to necrotrophic diseases (see BOX 2).

R-genes have typically been identified by a combination of approaches, including fine-mapping and positional cloning[21], mutation screening[22,23] and systematic identification and testing of NLR genes[24]. Fine-mapping, positional cloning and mutation screening are much more straightforward when resistance can be unambiguously distinguished from susceptibility on a single-plant basis. Such discrete phenotypes are more typical of qualitative resistance than of QDR (FIG. 1), and therefore R-gene cloning has been easier than QTL cloning. Identification using homology is obviously more feasible with traits for which there is an *a priori* indication of the family to which the causal gene likely belongs (in this case, qualitative resistance caused by NLRs) and is unsuited to traits for which the underlying genes are more diverse or less well understood (in this case, quantitative resistance). Thus, the identification and analysis of R-genes has proceeded more quickly than that for genes conditioning minor effects.

Recent advances in genomic technology are contributing to the identification of both R-genes and genes underlying QTLs. The increasing availability of

Durability
A property that enables resistance to remain effective when deployed over a large area under substantial disease pressure over a long time.

R-genes
Resistance genes of large effect that are inherited in a Mendelian fashion and typically, but not always, encode nucleotide-binding leucine-rich repeat proteins.

Genetic architecture
The number, locations and effects of genomic variants that give rise to phenotypic variation.

Pathosystems
Ecological subsystems defined by a specific disease. A plant pathosystem includes one or more host plant species along with the pathogen(s) that cause(s) the disease.

Effector protein
A protein that is secreted into host cells by a pathogen to suppress defence responses and alter other host biological processes.

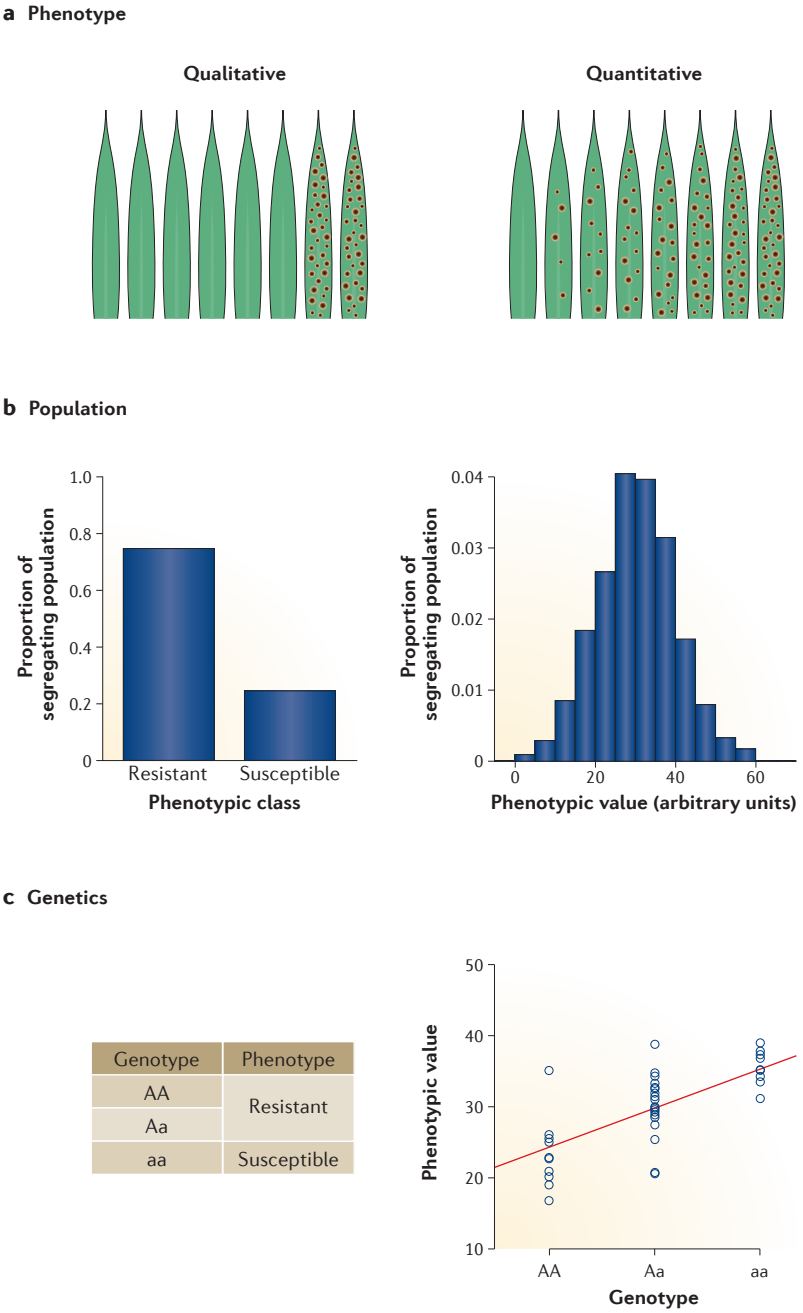

Figure 1 | **A comparison of quantitative and qualitative resistance. a** | At the phenotype level, two discrete classes are seen for qualitative resistance in a segregating population, while a continuous distribution is seen for quantitative resistance. **b** | In a segregating population, a dominant major gene conditioning qualitative resistance segregates in a 3:1 ratio, while multiple genes of small effect contribute to continuous phenotypic variation for quantitative resistance. **c** | For qualitative resistance, a single underlying gene will give rise to two distinct phenotypes: resistance or susceptibility. The segregation of a single gene for quantitative resistance has only a minor effect on the disease phenotype. The segregation of other quantitative resistance genes and environmental effects causes a range of resistance phenotypes. Figure adapted with permission from J. Poland, Kansas State University, USA.

sequence data combined with a deeper understanding of host–pathogen interactions might help to identify R-genes that are more likely to be effective for resistance breeding strategies. For example, one part of a proposed effector-targeted strategy[25] involves sequencing the existing pathogen population to characterize the relevant effectors and then deploying R-genes that recognize those effectors. Effector genes in a pathogen genome are usually identified using a combination of bioinformatic and functional approaches[26,27]. Once a set of putative or known effectors has been identified, they can be transiently expressed in the host to identify R-genes that lead to a resistance (hypersensitive) response[28,29]. Diverse germplasm (including wild relatives of crop species) can be screened for R-genes that recognize the effectors that are most important for pathogenesis.

Genes and mechanisms that confer quantitative resistance. Most studies on quantitative resistance in crop plants have focused on the underlying genetic architecture, which is directly relevant to crop improvement, rather than on the identity and mechanisms of individual genes[10,11]. To utilize the diversity of resistance mechanisms in a crop species, it is necessary to access and understand the genetic diversity of that crop. Germplasm collections set the stage for studies on the genetic diversity of resistance mechanisms and provide the raw material for resistance breeding (BOX 1). Such collections have been crucial in supporting efforts to control potentially devastating crop diseases such as the global potato late blight[30] and wheat rust[31] pandemics.

In crop plants, linkage analysis and genome-wide association studies (GWAS) have been used to identify the genomic loci influencing resistance phenotypes[10]. These techniques are often used to complement each other, as in the nested association mapping approach[32]. A typical quantitative resistance locus (QRL) identified through linkage analysis encompasses hundreds of genes, and many credible candidate genes may exist among them, making it very difficult to identify the true causal gene. GWAS provide much higher-resolution mapping and facilitate the identification of candidate genes for validation by transformation and/or mutagenesis[33]. Mapping studies reveal that resistance is often a polygenic trait (also known as a complex trait); that is, several genetic loci that contribute to the resistance phenotype segregate in any one biparental cross, which produces a continuous distribution of phenotypes (FIG. 1). Partially overlapping sets of resistance-conferring loci are typically identified in different crosses.

Large numbers of QRLs have been identified in well-studied crops, and over time, the resolution of loci has improved (that is, the size of a given locus in which a causal variant is known to reside has decreased). A synthesis of 16 mapping studies for diseases of rice found 94 QRLs that collectively covered more than half the rice genome[34]. In maize, a similar synthesis of 50 studies identified 437 QRLs covering 89% of the maize genome[35]. Subsequent QRL mapping in maize using a large multi-parental population[32] detected numbers of QRLs similar to previous studies for any given disease; however, many of the loci were mapped at much higher resolution[36–38]. Although many loci have been implicated in disease resistance, it is likely that many more remain

Box 2 | **Susceptibility genes**

Resistance can be caused by either the presence of a resistance gene (R-gene) product that confers resistance or the absence of a susceptibility gene (S-gene) product that confers susceptibility to the pathogen. A single copy of a susceptibility allele is typically sufficient to allow a pathogen to succeed, which is the scenario seen for recessive R-genes (thus, they can also be considered dominant S-genes)[7–9]. Some S-genes encode targets of host-selective toxins, such as those from *Cochliobolus victoriae* or *Periconia circinata*[145]. The widely used *mlo* gene for resistance to barley powdery mildew is a loss-of-function mutation of a negative regulator of the defence response[146]. In lines carrying only the recessive form of the gene, the defence response is readily triggered, enhancing resistance to some biotrophic pathogens but susceptibility to some necrotrophs. The *PMR6* gene, a pectate lyase-like gene in Arabidopsis, is required for susceptibility to powdery mildew[147]. In the case of rice bacterial blight, some host S-genes encode sugar transporters that pathogen effectors control to benefit the microorganism[148].

Whether a gene provides resistance or susceptibility can vary by pathosystem. Microbial effectors secreted by necrotrophic pathogens have been shown to interact with genes typically associated with defence and disease resistance (predominantly nucleotide-binding domain leucine-rich repeat containing (NLR) genes) to trigger host cell death, leading to susceptibility[149,150]. A wall-associated kinase (WAK) gene was shown to confer susceptibility to a necrotrophic pathogen of wheat, *Parastagonospora nodurum*[151], while another WAK was found to condition resistance to the hemibiotrophic pathogen of maize *Setosphaeria turcica*[14]. Remorin genes, which encode membrane-associated proteins involved in plasmodesmatal function, can also contribute to resistance or may be exploited by pathogens and thus contribute to susceptibility. One remorin gene acts as a resistance factor for potato virus X[152], another is implicated in resistance to a fungal pathogen in maize[153], and a third remorin gene acts as a susceptibility factor for *Phytophthora infestans*[154].

unidentified, possibly because the resistance alleles are either fixed in the population or their effects are too subtle or inconsistent to be detected using current methods (BOX 1).

The underlying resistance mechanisms are unknown for most QRLs, but the causal genes within a number of QRLs have been fine-mapped and cloned (TABLE 1 and Supplementary information S1 (table)). In some cases, multiple linked genes (such as groups of functionally related defence genes involved in secretory processes and cell wall reinforcement) have been shown to underlie a single QRL[34,39]. Many of the genes identified to date are similar in sequence to NLR genes, PRR genes or defence genes that can be controlled by these recognition-related genes. This is not surprising, because functional variation in these genes has been observed in several species[40,41]. Several other genes do not resemble R-genes but are involved in pathways known to be associated with plant defence; examples include genes that encode components of the phenylpropanoid pathway, which leads to production of small defensive molecules called phytoalexins and structural components of cell walls (such as lignin)[33]. However, other identified genes had not previously been associated with disease resistance or the defence response. Thus, these studies support the previously proposed idea that QDR might be based not only on the same mechanisms that underlie qualitative resistance but also on other, novel mechanisms[11,17] (FIG. 2).

Dimensions of effective resistance

Generating broad-spectrum resistance. Most R-genes are extremely specific and provide resistance against only one or a few strains or races of a particular pathogen. Some R-genes, especially NLR genes, are found in tightly linked clusters in plant genomes[42]. This clustering of NLR genes both allows and reflects evolutionary processes that enable diversification of the recognition specificities of R-genes[42,43]. That is, while most individual R-genes are highly specific, a cluster of genes at a complex locus can diversify in function and thus eventually confer resistance to different races of the same pathogen[44] and/or to multiple pathogen species[45].

Unlike R-genes, QRLs are generally race-nonspecific (although some QRLs do show race specificity[46]), and QDR that has been selected for a certain disease tends to provide resistance against diverse pathogen races that cause that disease[47]. Plant breeders value this broad-spectrum crop protection. Resistance that is effective against multiple pathogen species is even more valued, and genes conferring multiple disease resistance (MDR) also tend to be among the most durable[48]. Many genomic regions have been associated with resistance to multiple diseases[48]. However, until the causal genes are identified, it is usually not clear whether the MDR results from genetic linkage between distinct resistance genes (as seen in R-gene clusters) or from pleiotropy, where individual genes, such as *Lr34* in wheat, condition resistance to multiple diseases[48]. A single pleiotropic gene and a cluster of tightly linked genes can both be moved from one cultivar to another through traditional breeding, but a single gene may more easily be transferred through transgenic means.

Combining multiple R-genes and/or QRLs into a single genome usually improves its resistance phenotype. This approach is often called 'pyramiding' in the breeding literature and 'gene stacking' in the transgenic field[49]. Resistance genes can be combined to produce novel quantitative or qualitative phenotypes. While the combined effects of R-genes may or may not exceed the effect of the strongest gene[50–52], pyramiding of R-genes can improve the spectrum of resistance; genes with complementary resistance spectra can be selected such that gene pyramids provide resistance to a broad set of pathogen races[53,54]. By contrast, QRLs are generally additive in effect, although non-additive effects are also sometimes observed[52].

Specificity arises as a consequence of the evolutionary dynamics between hosts and their pathogens. New pathogen variants can arise that can overcome a defence strategy, for example, by modifying the ligand that is recognized by the host or by suppressing the host response to recognition[55,56]. The differential virulence of the new and old variants is influenced by the gene(s) underlying the defensive strategy and is reflected as strain specificity. If a resistant crop variety encounters the new pathogen variant, its resistance is partially or completely ineffective and the resistance is said to have broken down. The epidemiological consequences of this depend on the fitness of the new variant. Thus, the issue of specificity is related to the practical issue of durability.

Generating durable resistance through complexity. The importance of durable resistance in breeding programmes varies with context; long-lasting resistance

Nucleotide-binding domain leucine-rich repeat containing (NLR) genes
A family of plant genes involved in pathogen recognition. Many resistance genes of large effect are NLR genes.

Biotrophic pathogens
Pathogens that obtain nutrients from living plant tissue.

Necrotrophic pathogens
Pathogens that obtain nutrients from dead plant tissue.

Quantitative resistance locus
(QRL). A genetic region that has been statistically associated with quantitatively inherited resistance to a disease and that is presumed to contain alleles or genes that affect resistance.

Races
Variants within a pathogen species that elicit differential responses from resistance genes.

Genetic linkage
The co-inheritance of loci that are close together on a given chromosome.

Pleiotropy
A phenomenon in which one gene influences multiple traits.

Monogenic resistance
Resistance that relies on a single resistance gene.

Monocultures
Agricultural systems involving a single crop. The concept is used in contrast to systems that involve crop diversity in time and/or space, such as intercropping and rotation systems.

is important when varietal change is slow, but durability may be less critical in breeding programmes that regularly release new varieties with novel resistances[57]. Durability cannot be selected for directly in breeding programmes because it is defined in a retrospective fashion on the basis of its long-term performance[58]. Nonetheless, an understanding of host–pathogen biology and genetics can inform the design of resistance breeding strategies, crop varieties and deployment strategies to improve the likelihood of sustainable crop protection.

The durability of resistance is dependent on many factors, including the biology, genetics and evolution of the pathogen to which it confers resistance[59]. For an individual gene, durability is influenced by the ease with which its corresponding pathogen can either evade or suppress its resistance function. Monogenic resistance based on R-genes is often easily overcome by evolving pathogen populations[60], particularly when resistant plants are deployed in large monocultures. However, not all R-genes are equally vulnerable to being overcome. When a pathogen avoids recognition as the result of a mutation, it can incur a fitness penalty. This 'cost of virulence' (often equivalent to the cost of mutation) varies among effectors[61]. The stability of an R-gene is thus related to the physiological role and the evolutionary potential of the effector it recognizes. Indeed, certain qualitative resistance genes have been associated with durable resistance. For example, *Rpg1* was the only widely deployed stem rust resistance gene in barley for many years[62], and it provided high levels of resistance for roughly six decades[63] until it was overcome by recently emerged pathogen races. Similarly, the wheat gene *Lr34* has conferred effective resistance to multiple pathogens for a century[64]. *Lr34* encodes an ATP-binding cassette transporter rather than an NLR and provides incomplete disease resistance; thus, although typically regarded as an R-gene, it can actually be considered to be a strong QRL (TABLE 1).

It has been proposed that it might be possible to predict R-gene durability on the basis of knowledge of its cognate effector[65,66]. An R-gene is more likely to remain effective if it targets an effector that is critical for the survival or virulence of the pathogen[67], and such essential effectors might be identified on the basis of their high levels of conservation within the pathogen population[68] or on the basis of the fact that they target important plant proteins[69]. While it is not yet generally practical to implement these criteria in breeding programmes, it may become feasible as the techniques and data sets needed to identify effectors and corresponding R-genes improve[70].

Table 1 | **Examples of different types of causal and candidate genes that contribute to quantitative resistance**

Type of gene	Putative or presumed mechanism	Example pathosystems	Refs
Typical NLR	Recognition (ETI)	• *Pi35* (rice blast) • qBR4-2a (rice blast) • *RRS1* and *RPS4* (black rot, Arabidopsis) • *Rcg1 (Anthracnose stalk rot of maize)*	163, 164 165, 66
Atypical NLR	Recognition (ETI)	*PB1* (rice blast)	167
WAKs	Recognition (PTI)	• *WAK14* and several others from rice (rice blast) • *Wak* from maize (head smut of maize) • *Htn1* from maize (northern leaf blight of maize)	168, 169 14
RLKs	Recognition (PTI) and/or signalling	• *RFO3*, encodes a B-lectin RLK (fusarium wilt of Arabidopsis) • *pan1*, encodes an RLK with a leucine-rich repeat and an inactive kinase domain (northern leaf blight and Stewart's wilt in maize)	170,9
Other kinases	Signalling	• *Yr36*, encodes WKS1, a kinase with a steroidogenic acute regulatory-protein related lipid transfer domain (stripe rust, wheat) • *MPK6*, encodes a mitogen-activated protein kinase (rice bacterial blight and blast) • *RKS1*, encodes an atypical kinase (black rot, Arabidopsis)	171, 172, 173
CCCH-type zinc-finger protein	Transcription or RNA-level interference	*C3H12* (rice bacterial blight)	174
WRKY-type transcription factor	Transcription or RNA-level interference	*WRKY13* in rice (rice bacterial blight and blast)	172
Transporter	• Unknown • Inhibits hexose transport	• *Lr34*, encodes a protein that resembles ATP-binding cassette transporters of the pleiotropic drug resistance subfamily (resistance to multiple biotrophic diseases of wheat) • *Lr67* (resistance to multiple wheat biotrophic pathogens, three rusts and powdery mildew)	64, 175
Lignin synthesis	Resistance is associated with increased lignin synthesis	*CCoAOMT2* (resistance to the maize necrotrophic diseases grey leaf spot and southern leaf blight)	33
Other	Unknown	*PI21*, encodes a proline-rich protein with a putative heavy-metal-binding domain and protein–protein interaction motifs (rice blast)	176

See Supplementary information S1 (table) for additional information. ETI, effector-triggered immunity; NLR, nucleotide-binding domain leucine-rich repeat containing; PTI, pathogen-associated molecular pattern-triggered immunity; RLK, receptor-like kinase; WAK, wall-associated kinase.

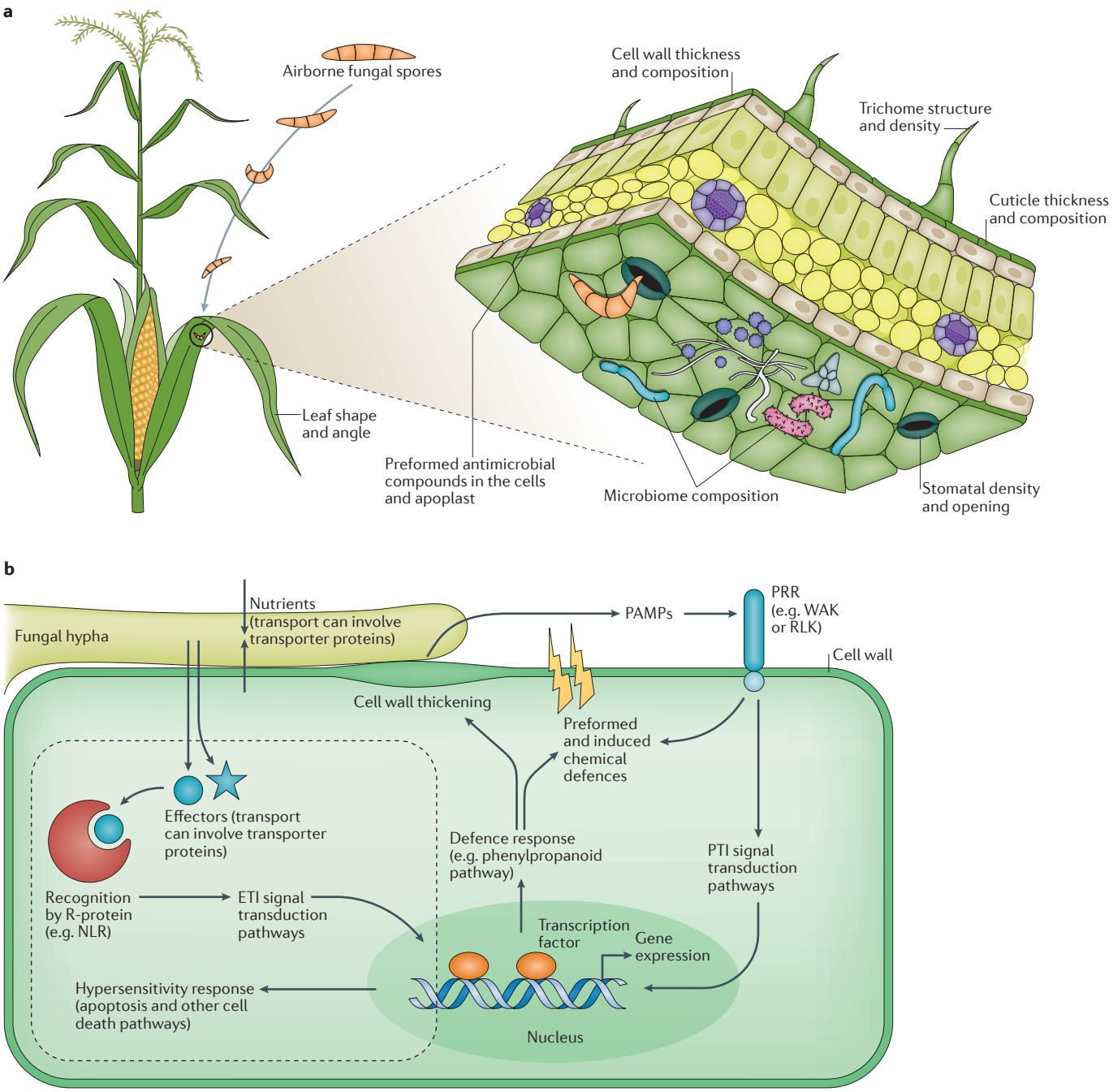

Figure 2 | **Resistance mechanisms at the tissue and cellular levels. a** | At the organismal and tissue levels, the success of a pathogen can be influenced by a range of features of the morphology, biochemistry and microbiome of the plant. **b** | At the cellular level, factors that affect the ability of a pathogen to infect its plant host include defence responses triggered by recognition events in the host via pattern recognition receptors (PRRs), such as wall-associated kinases (WAKs) or receptor-like kinases (RLKs), and resistance proteins (R-proteins), such as nucleotide-binding domain leucine-rich repeat containing (NLR) proteins; nutrient availability in the apoplast and cytoplasm; pre-existing chemical factors; and cell wall constitution. These factors are affected by host genotype and are potential causes of quantitative variation. Qualitative variation in resistance usually, though not always, occurs at the level of resistance gene–effector interactions. ETI, effector-triggered immunity; PAMPs, pathogen-associated molecular patterns; PTI, PAMP-triggered immunity.

At the genotypic level, genetic complexity influences the durability of resistance encoded by individual genes. For asexually reproducing pathogens, the presence of multiple resistance genes might, in principle, offer a greater evolutionary obstacle than a single resistance gene because a pathogen would have to develop mutations in all the effectors that are recognized by the resistance gene complement in order to overcome complex resistance[59]. Indeed, polygenic resistance associated with diverse defence mechanisms

is needed to provide long-lasting protection from pathogens that have the capacity to evolve rapidly[60,71], and there is increasing evidence that multiple mechanisms underlie both quantitative (TABLE 1) and qualitative resistance. In many pathosystems, varieties with proven durable resistance tend to carry resistance alleles at multiple QRLs and R-genes. For example, QTL analysis of a traditional rice variety known for its durable resistance revealed that it has resistance alleles at many R-genes and QRLs[72].

Experimental evidence regarding durability is limited because it can be demonstrated only when tested over large areas and long periods of time[58]. Nevertheless, it has been observed that the presence of quantitative resistance can increase the durability of qualitative resistance[73,74]. In the context of a genotype with complex resistance, a major gene can contribute to resistance without imposing a strong selection pressure for the development of compatible pathogen variants. The same is likely true for QRLs. However, while incorporating resistance gene pyramids into breeding strategies might improve durability of resistance[75], pathogens have mechanisms that can potentially allow them to evolve rapidly to overcome multiple resistance genes. Sexual reproduction or parasexual genetic exchanges among pathogen populations can produce novel combinations of genes, and mutations in gene clusters or in regulatory genes might also permit rapid adaptation that can make pyramiding less effective. Another complication of working with complex resistance is that alleles conferring QDR can be lost in the breeding process if major genes are present to mask their effect[76]. This risk has motivated some programmes to select against major genes during parts of the breeding process[77–79].

While there is little empirical evidence that the number of R-genes predictably increases durability, specific R-gene combinations may be more difficult than others for pathogens to overcome[80]. In the rice blast pathosystem, clonal lineages of the pathogen were found to have variable responses to some rice resistance genes and invariant responses to others[54]. The 'lineage-exclusion hypothesis' was based on the premise that these invariant responses reflect the evolutionary constraints of each lineage and that strategic combinations of resistances might provide durable resistance[53]. However, multiple R-genes do not always provide lasting resistance; some lineages of the potato late blight pathogen, for example, can overcome numerous R-genes[81]. The most reliable strategy for building durable resistance is to combine multiple minor QRLs. While their individual effects may be small, the combined effects of several minor QRLs can be considerable. Indeed, it has been suggested that a modest number ($n \approx 5$) of minor genes is sufficient to provide adequate resistance to Ug99 races of the wheat stem rust pathogen[31,82]. Furthermore, genes of subtle effect exert minimal selection pressure on pathogen populations, making them less likely to induce pathogen adaptation. However, although QDR is generally less vulnerable to breakdown than qualitative resistance, its durability is not absolute. Several studies have shown that pathogens can evolve to partially overcome or adapt to QDR; resistant germplasm can select for more aggressive pathogen strains, which cause more disease on both resistant and susceptible germplasm[83–88]. In a study on apple scab disease, pathogen strains were collected from apple lines with or without a certain quantitative resistance allele over several years. Pathogen strains from the apple lines carrying the resistance allele were more aggressive, yet the resistance remained effective over time, apparently because the more aggressive strains did not come to dominate the pathogen population[86]. Thus, it is likely that durability varies even among QRLs.

Managing pleiotropy and the trade-offs of resistance. Genes that play roles in resistance or susceptibility to pathogens might also affect other important traits, for example, yield or response to abiotic factors such as water or nutrient stress. In addition, resistance to one disease might be associated with resistance or susceptibility to another[48]. For both quantitative and qualitative resistance, it is likely that the trade-offs associated with different resistance alleles are quite variable because of the diverse roles that resistance-related genes have in plant growth and development[76]. Thus, an understanding of the pleiotropic effects of resistance loci is critical for crop improvement. Field-based breeding methods that involve a holistic assessment of plant performance across diverse environments can allow for effective management of trade-offs[56].

R-genes are sometimes associated with yield costs in the absence of the disease to which they confer resistance[89,90]. In a review of 88 studies involving disease resistance, 56% of the studies reported a cost of resistance, with the average cost being less than 5% of biomass and fecundity[89]. Some R-genes are fairly costly, such as the Arabidopsis R-gene *RPM1*, which incurs a 9% yield cost in the absence of the pathogen to which it confers resistance[90]. However, other R-genes seem to have no measurable costs to yield, and some are associated with positive effects on yield. Resistant and susceptible alleles of the gene *RPS2* in Arabidopsis do not have different effects on yield, while lines deleted for the gene have lower yields because the gene serves as a negative modulator of the defence response[91]. A locus associated with durable resistance to rice blast was found to contain multiple NLR genes, two of which showed opposing effects on resistance and yield; the epigenetic interactions between the genes led to resistance without compromising yield[92]. As most crop species carry 100 or more NLR genes[93], it seems likely that most R-genes have negligible impacts on yield potential.

Only a few studies have directly examined yield costs of quantitative resistance because it is difficult to separate the fitness cost of the QDR gene from the influences of linked genes. Analysis of specific alleles at particular genes will become possible as more isogenic QRLs become available or causal genes are isolated (BOX 3). Nevertheless, modest yield costs have been shown to be associated with resistance alleles at two QTLs for southern leaf blight resistance in maize in the absence of

Box 3 | **Near-isogenic lines**

Near-isogenic lines (NILs) are sets of genotypes that differ at one or a few genetic loci and are useful for quantitative trait locus (QTL) discovery, validation and/or characterization. While the effects of differing maturity dates, plant architectures, general adaptation or other differences can interfere with the assessment of resistance in diverse germplasm, NILs can be used to characterize contrasting chromosomal segments on a uniform genetic background. NILs are typically produced by transferring ('introgressing') one or more chromosomal segments from a resistant genotype into the genetic background of a susceptible line. Various types of NILs can be produced using different crossing strategies: a single locus can be introgressed by backcrossing[155]; a large number of loci can be introgressed, such that the different introgressions span an entire region or chromosome[156]; or lines near the end of the inbreeding process that harbour residual heterozygous regions can be self-pollinated to produce NILs contrasting at those regions[157]. Transgenic lines, genome-edited lines and mutants can be considered NILs relative to their respective control genotypes.

NILs enable detailed analyses of chromosomal segments carrying resistance loci (resistance genes (R-genes) and quantitative resistance loci (QRLs)). For example, NILs have been used to characterize the resistance spectra of R-genes[158], and sets of maize NILs carrying introgressions from resistant lines into susceptible backgrounds were used to identify QRLs conferring resistance to single and multiple diseases[155,159]. NILs are also useful for validating QTLs defined by linkage or association mapping; for example, only three of 17 loci identified through genome-wide association studies as putative QTLs for accumulation of the mycotoxin deoxynivalenol were validated in the corresponding NILs[160].

NIL studies also allow for dissection of resistance components. In a set of NILs differing in alleles affecting barley stripe rust, individual QRLs varied in their relative effects on different resistance components[161]. A NIL population was used to determine that resistance alleles at different QRLs affected different stages of pathogenesis of a maize fungal disease[162].

Most NILs are created through a few generations of backcrossing and, therefore, at any region of interest, several linked genes are likely to have been introgressed from the donor line. This fact is of particular importance in the analysis of possible pleiotropic effects associated with a resistance locus. For example, if the resistant NIL shows an undesirable trait such as low yield, it is not readily obvious whether the genes conferring resistance are the same as the yield-reducing genes.

disease, while modest yield benefits were observed in the presence of the disease[7]. In *Brassica rapa*, growth costs were associated with quantitative resistance to downy mildew, but not to blackleg disease[94]. As for R-genes, the costs of resistance seem to be variable for QDR.

Plant breeders take the trade-offs and benefits associated with pleiotropic effects into account when they breed for resistance, often selecting for effective forms of resistance with low fitness penalties without requiring knowledge of the mechanisms at play[76]. That said, in some cases, the mechanisms underlying pleiotropy are known. For example, activation of the HR or other forms of programmed cell death that confer resistance to biotrophic pathogens can also confer growth penalties. The gene that encodes ACD6 in Arabidopsis increases resistance to a number of pathogens but also causes extensive leaf necrosis, slows growth and reduces biomass[95]. The widely deployed and durable *mlo* powdery mildew resistance gene in barley is associated with necrotic flecking and yield loss[76,96] as well as susceptibility to several necrotrophic diseases through its role in modulating the defence response[97]. Leaf flecking in maize has also been associated with increased resistance to many diseases but often reduces yield[98]. The major gene XA4 in rice, which provides resistance to some races of the bacterial blight pathogen *Xanthomonas oryzae* pv. *oryzae*, encodes a WAK that provides several beneficial traits in rice[99]. The gene provides resistance by promoting cellulose synthesis in a way that strengthens the plant and reduces its height without reducing yield. Even when overcome by virulent races of *Xanthomonas oryzae* pv. *oryzae*, XA4 provides 'residual' resistance[100] and provides agronomic benefits, so the gene is widely deployed in rice breeding programmes. A locus identified as a QTL for a maize disease was also associated with an effect on maturity[11]. Whether this is beneficial or otherwise would depend on the breeders' or farmers' needs and objectives.

Given the potential trade-offs between resistance and yield, it is possible that selection for increased yield in the absence of appropriate selection for disease resistance may inadvertently select for increased susceptibility in some cases, as was first suggested more than 50 years ago[101]. Conversely, yield and other agronomically important traits should be considered when selecting for resistance. A greater understanding of the mechanisms underlying resistance and susceptibility, and the roles of these genes in biological processes that determine other plant traits, will allow for better targeting of resistance breeding efforts.

Methods for breeding better resistance

As argued above, breeding programmes aiming to produce varieties with strong and durable disease resistance should combine diverse resistance loci (quantitative and qualitative) that have minimal adverse effects on other desired traits. While single R-genes are often non-durable, they can contribute to crop protection when combined with QDR[73]. Although creating complex resilient forms of resistance is generally more difficult than creating simpler, more fragile forms, it is feasible to assemble polygenic resistance through phenotypic and/or genotypic selection[3]. Transgenics and/or genome editing can also contribute to producing desired allelic combinations.

Selection methods for QDR. Many modern breeding programmes rely largely on recycling of elite lines to generate new ones. This narrowing of the gene pool has led to long-standing concerns about the potential erosion of diversity and of resistance[102]. Novel resistances are needed as new disease problems arise. Although non-elite germplasm often contains an abundance of disease

Elite lines
Crop genotypes that have been selected for high performance in a breeding programme, often re-used as parents for further breeding cycles.

resistance traits[48], such material can also carry many undesirable alleles, which challenges breeding pipelines and can complicate the identification of resistance.

A range of genetic mapping designs empowered by genome sequencing technologies are now available that can facilitate rapid identification of large-effect QRLs[10], which in turn can be leveraged for marker-assisted selection. New varieties with single major genes can be generated by backcross breeding, often assisted by genetic markers. However, it can take several years and multiple generations to introgress a single QRL of large effect from non-elite germplasm into elite germplasm while minimizing linkage drag (that is, the undesirable traits associated with genes linked to the target gene)[103]. Therefore, approaches that support prediction or early identification of emerging pathogens and corresponding QRLs before epidemics occur are crucial.

Generating polygenic resistance by introgressing multiple loci, each of small effect, can be even more challenging than transferring monogenic resistance; enormous numbers of plants need to be assessed because useful recombination and favourable assortment events occur with low frequency. This constraint can hamper the ability of breeders to deploy durably resistant and high-yielding cultivars[103]. However, varieties with complex resistance can be created through a range of breeding methods, including recurrent selection. Recurrent selection is a reliable method for accumulating favourable alleles, including those of small effect. In this approach, diverse sets of parents carrying complementary sets of genes undergo repeated cycles of recombination and selection. Because complementary gene sets can be enriched to yield stronger resistance, there is the potential for transgressive segregation at each cycle. Recurrent selection is useful for achieving breeding objectives involving quantitative inheritance, low heritability and multiple traits (for example, various components of resistance, such as resistance to penetration, incubation period and lesion size) and has been effectively applied to improve quantitative resistance to various diseases, such as northern leaf blight of maize[104] and downy mildew of pearl millet[105].

Genomic selection is another strategy that allows breeders to select for traits that are influenced by large numbers of small-effect alleles[106]. This approach uses high-throughput genotyping to ascribe a breeding value to alleles at thousands of loci throughout the genome and to predict the individuals with the best allelic combinations. Selections can be made from phenotype predictions for large numbers of progeny, and multi-trait indices can be developed to simultaneously select for disease resistance and agronomic traits. Genomic selection can be used to screen germplasm in gene banks[107] and can increase the efficiency of selection by allowing it to be practised in environments where the disease is not present. This approach is most relevant when genotypic (that is, DNA sequence) data are less costly to generate than collecting phenotypic (disease) data, which is the case in many contexts[106,108]. Genomic selection has been successfully implemented for a number of diseases in small grains, maize and cassava[106]. The emerging field of high-throughput phenotyping is likely to facilitate breeding for complex resistance by enabling many aspects of the plant resistance response to be screened simultaneously[109].

Transgenic and genome editing methods. Transformation and gene editing have the potential to contribute to general plant improvement and to improving disease resistance in particular. In principle, these methods allow R-genes, QDR diversity and modified S-genes from the entire plant kingdom to contribute to the resistance of plants amenable to gene transfer techniques. The potential utility of these techniques for crop protection is demonstrated by a number of successful examples of transgene-conferred resistance, many of which involve transfer of R-genes within and between plant species[25]. Indeed, multilines produced by transgenic means have been shown to improve the performance of individual resistance genes[110]. However, while transgenic plants have been grown in production agriculture for 30 years on increasing areas, very few disease-resistant transgenic plant varieties have been commercially released. The reasons for this lack of availability are complex but include issues relating to intellectual property rights, complex regulatory restrictions (some reflecting public concerns about biosafety), a lack of efficacy related to a range of technical challenges, unwanted pleiotropic effects and insufficient commercial benefit to offset development costs[111].

New genome editing techniques promise to simplify the process of gene deletion, editing and insertion in plants from a technical, and potentially from a regulatory, perspective. Available technologies include zinc-finger nucleases, TAL effector nucleases (TALENs) and the CRISPR–Cas9 system. Their use for plant improvement has recently been reviewed[112]. The availability of genome sequences from an increasing number of plant species means that gene targets are fairly easy to identify. Genome editing can be used to modify the DNA sequence of a single gene in order to alter or disrupt its function. It can also be used to insert multiple genes as a single unit or 'cassette' for ease of transmission to further generations by genetic crosses, as has been demonstrated for two herbicide tolerance genes in maize[113]. Genome editing should be considered as complementary to traditional breeding.

Genome editing has been used for targeted disruption of several susceptibility loci. Both TALENs and CRISPR–Cas9 were used in wheat to edit homeoalleles of *mlo*, which encodes a susceptibility factor for powdery mildew[114]. Disruption of the eukaryotic initiation factor locus, which promotes susceptibility to several potyviruses, improved resistance to several viruses in cucumber[115] and Arabidopsis[116]. In rice, resistance to bacterial blight was achieved by TALEN-mediated disruption of a sucrose efflux transporter gene[117], and CRISPR–Cas9-induced mutations in a rice ethylene responsive factor gene conferred resistance to blast[118].

The Cas9 protein itself evolved as part of the bacterial immune system to destroy foreign nucleic acids, such as invading viral or plasmid DNAs[119–121]. This function can be co-opted by plant breeders to destroy invading pathogens in plants. Transgenic plants expressing Cas9

Cultivars
Cultivated varieties (genetic strains) of a domesticated crop plant.

Transgressive segregation
A phenomenon in which the progeny derived from a cross have more extreme phenotypes than either parent.

Multilines
Mixtures of plant cultivars that are genetically very similar but differ in their resistance genes that are grown together in a single plot.

Homeoalleles
Alleles of a gene or locus present in the homeologous chromosomes of a polyploid species.

Intercrops
Agricultural systems involving multiple crops in a single plot.

Cultivar mixtures
A mixture of multiple plant cultivars of the same species that are not necessarily closely related and are grown together in a single plot.

and single guide RNAs (sgRNAs) targeting geminivirus sequences have been used to confer resistance to a range of geminiviruses in *Nicotiana benthamiana* and *A. thaliana*[119–121]. Such approaches have the advantage of being highly flexible, as new sgRNA constructs can be designed if and when a target viral sequence mutates.

Breeding and multilevel diversity

Plant breeding can help to reduce crop losses by introducing diversity at multiple levels of agricultural systems (FIG. 3). Diversity at the plot and landscape levels remains the norm in much of the world's smallholder and organic agriculture, and it has the potential to improve the sustainability of agriculture worldwide by reducing pest pressures and increasing yields[122–125]. By comparison, monoculture is the norm in modern industrial production systems, and although it has resulted in unprecedented productivity, it is also a major driver of crop losses[126]. A large monoculture puts heavy selection pressure on pathogen populations because it provides any variant that overcomes resistance with a large number of hosts on which to reproduce. By contrast, genetic complexity at the population level can reduce the evolutionary dynamism of pathogen populations.

Modelling has been used to explore theoretical aspects of resistance durability when deployed in either pure populations or mixed populations[127–129]. For example, modelling shows that mixed populations of plants with monogenic resistance, arrayed in random patterns, can effectively reduce selection for pathogen populations that overcome resistance[123,127,129]. Host population diversity reduces the damage inflicted by pests and disease in a number of ways. For example, reducing the density of a given genotype alleviates selection pressure on the pathogen, barrier effects between different resistance genotypes prevent the spread of the pathogen, and diversity provides the opportunity for systemic acquired resistance to develop[123,130–132].

Population diversity can be classified as interspecific or intraspecific. Interspecific diversity can be achieved through use of intercrops or rotations, and intraspecific diversity can be generated by using cultivar mixtures or multilines[123]. Where the introduction of interspecific diversity through intercropping is feasible and desirable, it is important to identify combinations of germplasm that work well together as intercrops[133]. Breeding can improve the productivity, adaptation and resistance of intercrop components and their synergies[134]. However, it is important to recognize that the systematic use of diversity to reduce disease pressure in industrial agriculture would require the implementation of substantial changes. Intraspecific diversity for certain agronomic traits (such as maturity, plant morphology and quality) can pose problems in market-oriented, mechanized agriculture; markets demand uniform products, and farm equipment is designed for use on uniform crop types. Plant breeding can alleviate some of these issues by producing populations that are uniform for desirable traits but heterogeneous for traits such as disease resistance, for which uniformity is a liability[123]. This goal has been achieved for grains in small breeding programmes in various parts of the world[123].

Conclusions and future perspectives

The diversity of pests and their ongoing evolution makes breeding to improve plant resistance non-trivial. Moreover, breeding programmes do not always prioritize resistance traits because resistance breeding is inherently difficult and can detract from efforts to improve yield, quality and agronomic adaptation[135]. As a result, pesticides become the default option for crop protection despite widely acknowledged downsides that include toxicity to non-target organisms and loss of effectiveness due to pathogen evolution[136].

R-genes have larger effects than QDR and are therefore easier to study and to manipulate in breeding programmes. Although resistance breeding programmes often go beyond the sole use of R-genes to build high levels of quantitative resistance, they must do so more frequently if durably resistant crop cultivars are to be reliably

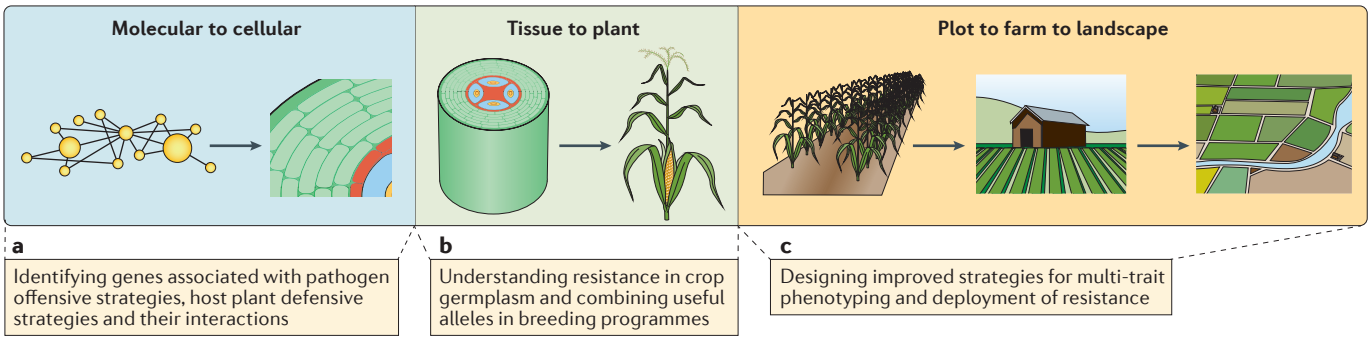

Figure 3 | **Challenges for designing sustainable disease resistance at different scales. a** | On the molecular to cellular scales, current research is leading to the identification of pathogen and host genes that influence disease outcomes, shedding light on offensive and defensive mechanisms at play in host–pathogen interactions and co-evolution. **b** | Understanding the genetic architecture of resistance as it influences resistance in different plant tissues and gene pools is allowing breeders to more strategically manage resistance in breeding programmes. **c** | Increasingly sophisticated phenotypic methods are allowing geneticists and breeders to understand the genetic trade-offs involved in different defence strategies. Use of diverse forms of resistance at the plant, plot and landscape levels can increase the effectiveness and sustainability of resistance.

produced for systems with high disease pressure and evolutionarily dynamic pathogens. Fortunately, advances in genomic technologies mean that QDR is now easier to study, which is providing a more holistic understanding of plant defence. Genes associated with QRLs that have been identified thus far suggest that novel mechanisms and useful alleles for disease resistance will be discovered as more effort is invested in understanding QDR.

Durability is influenced by host factors at the gene level as well as on the genotypic and population levels. All these factors have important implications for plant breeding; some genes are inherently easier than others for pathogen populations to overcome, but their context will influence the length of time that this will take. Durability is also influenced by the evolutionary potential of the pathogens[59] and the conduciveness of the environment[57]. While durable resistance is an important breeding objective, it is critical that the issue of sustainable disease resistance is not approached simply as a plant breeding problem. The deployment of heterogeneous (including intercrop and similar) populations can be effective in reducing pathogen evolution. Thus, host diversification is both an important complement to breeding and an important contextual factor for breeders to consider.

Genomic tools are greatly empowering the processes of genetic analysis and crop improvement. Large-scale sequencing capacity allows breeders to better understand the structure and diversity of the genetic resources (germplasm collections) that provide the raw material for the development of new germplasm. A deeper understanding of the genes and pathways involved in resistance can inform strategies for the design of less vulnerable genotypes. In this regard, metabolomics, integrated with transcriptomics and genomics, is beginning to shed light on the diversity of molecular machinery that plants deploy for their defence[137]. The hundreds of thousands of compounds associated with plant defence are relevant targets for crop improvement and are often important for flavour and nutritional quality[138]. Genomic tools are also revealing the nature and function of the plant and soil microbiomes, and plant breeding further has the potential to produce crops that support microbial populations that in turn contribute to plant health[139,140]. New phenotyping technologies complement genetic ones: high-throughput methods might allow breeders and geneticists to evaluate many traits in parallel, allowing disease phenotyping to be integrated into more stages of selection[109].

While new technologies hold promise, a pragmatic balance must be struck between them and the basics of plant breeding. Investment in technological advances that empower genetics and breeding is, ironically, a potential threat to practical crop improvement if it leads to a reduced investment in the curation of genetic resources, crossing programmes, multi-environmental trials and other necessary stages in the plant breeding process. Plant breeding should be seen as one part of a wider strategy to develop a more sustainable agriculture that involves diversification and adaptation to changing climates and food systems.

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