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REVIEW ARTICLE

Advances in Durable Resistance to Diseases in Staple Food Crops: A Review

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Abstract:

Background:

At all stages of their development, plants are in permanent contact with causative agents of various diseases. Mechanisms of disease resistance and its durability in crops largely depend on the pathogen's lifestyle, namely the nutrition mode and host range.

Objective:

The objective of this review is to consider the main advances in the production of genotypes with durable disease resistance in the globally important food crops, wheat, rice, and potato, as well as barley.

Results:

In wheat, durable resistance could be provided by the employment of various adult plant resistance genes against biotrophic pathogens, whose action commonly does not involve hypersensitivity response, as well as major quantitative genes, including mutants of susceptibility alleles, against necrotrophs *via* marker assisted selection (MAS). In barley, the most prominent example is the gene *mlo* conferring durable powdery mildew resistance, but it is compromised by higher susceptibility to some necrotrophic fungi. A few genes for broad-spectrum resistance against the rice blast and bacterial blight pathogens confirmed their effectiveness for decades, and they could be combined with effective R genes *via* MAS. Resistance to late blight of potato is mainly provided by R genes introgressed from wild potato species, which could be pyramided with quantitative trait loci. Genes for extreme resistance to potato viruses derived from related species provide durable and broad-spectrum resistance and could be effectively deployed in potato breeding using MAS. Silencing susceptibility genes by genome editing technologies is the most promising approach to produce plants with durable resistance to many pathogens in the crop species. Genetic transformation with genes for resistance-associated proteins or constructs providing silencing *via* RNA interference is an effective biotechnological method to generate plants with durable resistance against pathogens, especially viruses.

Conclusion:

Main advances in the production of crop plants with durable resistance are based on studies of molecular mechanisms of plant immunity and its special features for pathogens with different lifestyles *via* the use of biotechnological approaches such as MAS for pyramiding of monogenic quantitative resistance genes or qualitative R genes, changes in expression of certain genes associated with resistance, the introduction of transgenes, mutagenesis and genome editing aimed at silencing susceptibility genes.

Keywords: Durable resistance, Pathogen, Wheat, Barley, Potato, Rice.

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1. INTRODUCTION PLANT IMMUNITY MECHANISMS WITH CONSIDERATION FOR PATHOGEN'S LIFESTYLE

Although the main goals of crop breeding are high yield and quality, they cannot be attained without consideration for disease and pest resistance. At all stages of their development, plants are in permanent contact with causative agents of various diseases, in particular fungi, viruses, oomycetes, and bacteria, as well as with pathogenic nematodes. The primary barrier against pathogens may be presented by morphological features such as plant architecture, waxes, trichomes, stomata distribution *etc*. However, detailed analysis of such traits revealed their low genetic potential for durable resistance

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breeding, especially for specialized pathogens [1].

Molecular strategies of disease resistance in plants largely depend on the pathogen's nature [2]. Depending on their nutrition mode, plant pathogens are divided into biotrophs, necrotrophs, and hemibiotrophs. Biotrophs feed on living cells, whereas necrotrophs require dead tissues for nutrition. Hemibiotrophs show both types of nutrition requirements at different developmental stages. Another feature influencing disease resistance mechanisms and resistance durability is host range, which varies from a broad one, when phytopathogens affect many plant species (generalists), to a narrow one (specialists) [3, 4].

Current models of plant immunity generally include two main tiers of the plant immune system [5 - 8]. The first tier involves the perception of elicitors, so called pathogen-associated molecular patterns (PAMPs) or microbe-associated molecular patterns (MAMPs) (cell wall components, enzymes, toxins *etc*.) [9]. These patterns are recognized by pattern recognition receptors (PRRs) located on the cell surface: PRRs often possess leucine-rich repeats in the extracellular domain and belong to receptor-like kinases containing an extracellular domain, a transmembrane domain and a cytoplasmic kinase domain or to receptor-like proteins lacking the cytoplasmic kinase domain [10]. These receptors account for pattern-triggered immunity (PTI) [5, 7, 8]. Damage of cells by necrotrophic pathogens can produce damage-associated molecular patterns (DAMPs) (cell wall polysaccharide fragments, apoplastic peptides and proteins, extracellular nucleotides, cutin monomers, extracellular sugars, extracellular amino acids, and glutathione) [11]. DAMPs are perceived by wall-associated kinases, which, like PRRs, possess an extracellular DAMP-binding domain and a cytoplasmic kinase domain [8]. PTI is considered to confer broad-spectrum and race-nonspecific resistance [10].

In addition, it was detected that some plant-parasitic nematode groups produce pheromones named ascarosides, which are recognized by the plant defense system as signaling molecules with nematode-associated molecular patterns (NAMPs) [12, 13]. NAMPs trigger the activation of innate immune responses in plants and enhance resistance to viruses, bacteria, fungi, oomycetes, and root-knot nematodes in some plant species [12].

The second tier of the plant immune system involves intracellular receptors with a central nucleotide-binding (NB) domain and a C-terminal leucine-rich repeat (LRR) domain (NLRs or NB-LRR proteins) detecting effectors (race-specific elicitors) produced by specialized pathogens [5 - 8]. There are two major types of NLRs depending on their N-terminal domain: the coil-coiled (CC) type (CNLs) and the Toll/interleukin-1 receptor-like (TIR) type (TNLs), TNLs being absent in monocots and some dicots, *e.g*., *Beta vulgaris* L. [14]. NLRs account for effector-triggered immunity (ETI). NLRs are products of classical R genes in Flor's gene-for-gene model in the case of biotrophic pathogens [15, 16], where effectors are avirulence factors.

Both pattern receptors and NLRs initiate signaling cascades involving multiple participants – mitogen-activated protein kinases, hormones, calcium, G-proteins, ubiquitin, and transcription factors, triggering the expression of genes for defense responses. Such responses include hypersensitive response, production of reactive oxygen species, cell wall enforcement, and production of various resistance-related proteins and metabolites [7, 8, 17].

Although many responses involving activation of the surface and intracellular receptors are similar, in contrast to NLRs, PRR activation is not associated with programmed cell death, and the defense responses caused by them are not so prolonged [6, 18]. In addition, recent investigations of resistance against the bacterial pathogen *Pseudomonas syringae* in *Arabidopsis thaliana* L. have demonstrated the mutual potentiation between the PRR and NLR recognition-dependent defense pathways to activate strong defense against the pathogen [19].

According to the invasion model of Cook *et al*. [20], both elicitors and effectors are considered invasion patterns (IP), which are detected by plant IP receptors triggering different IP responses depending on the pathogen's (invader's) nature. As to the circular model of the plant innate immune system of Andolfo and Ercolano [21], hormone-regulated signaling defense pathways play a central role in plant immunity modulation, resulting in the resistance response specific to the pathogen's lifestyle. Among plant hormones, salicylic acid (SA) is the main hormone involved in resistance responses to biotrophic and hemibiotrophic pathogens acting *via* the product of the nonexpressor of pathogenesis-related genes 1 (NPR1) as a transcriptional activator of defense-related genes [2], whereas NPR3/NPR4 act as redundant transcriptional repressors [18]. Another important hormone that works along with SA in both local and systemic immunity is N-hydroxypipecolic acid [18], which plays a key role in SA biosynthesis. Jasmonic acid and ethylene are major hormones involved in plant response to necrotrophic pathogens [2].

Defense against biotrophic pathogens is largely based on gene-for-gene resistance due to R genes (NLRs), which commonly leads to hypersensitive response – a rapid localized cell death at the pathogen penetration site restricting biotrophic pathogen's access to water and nutrients [2, 17]. On the contrary, for necrotrophs, programmed cell death is beneficial as they exploit this mechanism through NLRs for their expansion. According to Mengiste [22], toxins, necrosis-inducing proteins and related molecules are equivalents of effectors in necrotrophs. The necrotrophic fungi *Parastagonospora nodorum* and *Pyrenophora tritici-repentis* produce the effector Toxin A, which causes susceptibility in wheat lines with the toxin sensitivity gene *Tsn1*. *Tsn1* encodes a disease resistance gene-like protein with serine/threonine protein kinase and NB-LRR domains [23]. Thus, this NLR is required for susceptibility to the pathogens, whereas inactive alleles of *Tsn1* provide insensitivity to Toxin A. In addition, *Tsn1* also accounts for sensitivity to Toxin A produced by the necrotrophic fungus *Bipolaris sorokiniana* [24, 25]. Another well-known example is the *A. thaliana* gene *LOV1*, which encodes a typical NLR and confers sensitivity to the fungal toxin victorin, an effector of the necrotroph *Cochliobolus victoriae* required for pathogenesis [26]. Victorin binds to

thioredoxin TRX-h5, activates *LOV1* and elicits host cell death, thus conferring disease susceptibility. So, depending on the lifestyle of the pathogen, the role of ETI in resistance may be ambiguous.

It is ETI provided by NLRs (R genes) associated with the hypersensitive response that is referred to as qualitative resistance, or vertical resistance considered in terms of complete resistance or susceptibility [7, 27]. Quantitative resistance is defined as resistance expressed in the reduction of the disease rather than its absence [27] or reduced susceptibility [7]. NLRs generally provide race-specific resistance, whereas quantitative resistance is race-nonspecific, and some quantitative resistance genes may provide resistance against multiple pathogens. Poland *et al*. [27] considered qualitative and quantitative resistance as only two ends of the continuum with R genes and quantitative resistance loci lying towards each end of the spectrum, as implied by the phenomenon of residual resistance of some defeated classical R genes [28 - 31]. Moreover, according to Kushalappa *et al*. [7], all genes involved in plant defense processes may be considered R genes (genes responsible for the synthesis of resistance proteins and resistance metabolites) and thus employed for plant improvement.

The most important practical question is the durability of disease resistance. According to Johnson [32], durable resistance is resistance that remains effective while a cultivar possessing it is widely cultivated. Nicks *et al*. [33] proposed the revision of this definition as resistance that remains effective with the deployment of a certain R gene (combination). Parlevliet [3] considered durable resistance as a quantitative trait ranging from not durable (ephemeral or transient) to highly durable. Ephemeral resistance occurs against specialists – fungi, oomycetes, and bacteria of biotrophic and hemibiotrophic nature with high evolutionary potential when resistance is largely mediated by R (NLR) genes causing the hypersensitive response, and pathogens regain their virulence due to a loss mutation in a respective avirulence (effector) gene [3, 34]. Durable resistance against biotrophic and hemibiotrophic phytopathogens is, for the most part, quantitative, without a hypersensitive response. Resistance against generalists (pathogens with a wide host range) is durable and quantitative in nature. Resistance against pathogens with intermediary host range is also considered more durable than that against specialists [3]. On the contrary, resistance against viruses is often durable, irrespective of the level of specialization, even if resistance is monogenic by the hypersensitive type *via* NLRs [3, 35], largely due to the small size of the viral genome and low fitness of genotypes with mutations for avoiding resistance genes.

Thus, qualitative R genes against evolutionarily active pathogens are frequently defeated after their large-scale deployment. A prominent example is the massive use of bread wheat cultivars with the wheat-rye 1BL.1RS translocation from the rye Petkus, which shortly led to the global defeat of disease resistance genes on this translocation: the leaf rust resistance gene *Lr26,* the powdery mildew resistance gene *Pm8,* and the stripe rust resistance gene *Yr9* [36 - 38]. On the contrary, the stem rust resistance gene *Sr31* on 1BL.1RS remained effective for about 30 years against all stem rust races until the appearance of races of the Ug99 lineage, first described in 1999 in Uganda [39]. In addition, *Sr31* further remained important for European countries, as was demonstrated by the outbreak of the highly virulent stem rust race TTTTF (later named TTRTF) in Sicily [40]. This race shows complex virulence but is avirulent to *Sr31,* and it appeared in 2014 in the territory of Georgia, which turned out to be a hot spot for the formation of new stem rust races *via* sexual recombination [41]. TTRTF was also detected in Eritrea in 2016 and in the south of Iran in 2019 [42]. *Sr31* also provided resistance against recent stem rust races revealed in Germany [43]. However, in a short time, a new stem rust race with virulence to *Sr31*, TKHBK, appeared in Spain [44]. So, the lack of durability of important R genes presents a permanent problem for crop cultivation on a global scale, implying the search for new approaches to provide durable resistance. Main advances in the production of genotypes with durable disease resistance are associated with insights into molecular mechanisms of plant immunity and the use of biotechnological approaches such as marker-assisted selection (MAS), employment of monogenic quantitative resistance genes, including adult resistance genes, alterations of expression of certain genes associated with resistance or introduction of foreign genes *via* transgenic plant production, mutagenesis, including that for silencing susceptibility alleles, and genome editing. In this paper, results of studies for providing durable resistance will be considered for globally important food crops such as wheat, rice, and potato, as well as for barley. Wheat, rice, and potato are leading crops grown for human consumption on a global scale (Table **1**) [45, 46]. Their proportion used for human food is the highest among all the crops and comprises about 66% for wheat, 67% for potato and as high as 82% for rice. As can be seen from Table **1**, their consumption per person in 2019 was 65.9, 32.4, and 80.5 kg, respectively [46]. For comparison, in 2019, the consumption of such an important crop as maize was much lower, 19.02 kg per person and the food proportion of this crop was only about 13% [46].

Table 1. Global production and food consumption of wheat, rice, potato, and barley in 2019.

Crop	Harvested Area (ha)	Yield (Tonnes/ha)	Production (1000 Tonnes)	Food (1000 Tonnes)	Food Proportion (%)	Food Supply Quantity (kg/capita/yr)
Wheat	219006893	3.54	765867	504621	65.9	65.94
Rice	161771753	4.61	753411	616308	81.8	80.54
Potato	16475816	21.5	370673	248014	66.9	32.41
Barley	51018550	3.11	158951	7725	4.9	1.01

Source: FAOSTAT [45, 46]

Table 2. Yield losses caused by some major diseases in wheat and barley.

Crop	Crop Losses from a Disease (%), Reference					
	Leaf Rust	**Stem Rust**	**Stripe Rust**	**Powdery Mildew**	**Fusarium Head Blight**	**Viral Infections**
Wheat	up to 72 [49]	up to 100 [50], up to 47.9 [51]	up to 64 [52], 5-50 [49]	up to 55 [49]	up to 80 [53], up to 75 [49]	up to 84 [54]
Barley	15-50 [48]	10-50 [48]	25-55 [48]	10-40 [48]	5-15 [48], up to 71 [53]	up to 64 [54]

2. WHEAT AND BARLEY

Diseases contributing to serious yield losses in wheat and barley on a global scale predominantly include rusts, blotches and head blight, as well as powdery mildew and viral infections [47, 48]. Yield losses from some major diseases are summarized in Table **2**. However, as mentioned above, fungal biotrophic pathogens show the highest evolutionary potential, and resistance to such pathogens is commonly non-durable, in contrast to resistance to necrotrophs [3]. This part of the review considers different approaches for providing durability of resistance to mainly biotrophic pathogens. In addition, cases of ambiguity of resistance are described when a gene providing resistance to a disease at one developmental stage confers susceptibility either at another stage or to another pathogen.

2.1. Durable Resistance against Fungal Pathogens

Among a vast diversity of resistance genes to the most widespread biotrophic pathogens of wheat causing leaf rust (*Puccinia recondita*), stem rust (*P. graminis* sp. *tritici*), stripe rust (*P. striiformis* var. *tritici*) [45], and powdery mildew (*Blumeria graminis*), most of the genes are "classical" qualitative race-specific R genes, with a low durability potential [55]. These genes are referred to as major genes or seedling or all-stage resistance genes as they could be effective at all growth stages, from seedlings to adult plants. A much smaller group is represented by race-nonspecific resistance genes, which provide only moderate but durable resistance. Such genes are called adult plant resistance (APR) genes, as they commonly provide resistance only in adult plants [56, 57]. Due to their effect on the development of rust fungi, they are termed slow-rusting genes as they are associated with the prolonged latent period of development of the disease, the smaller number and size of uredinia in the first two weeks after the infection in comparison with plants lacking the APR [56]. Another beneficial feature of certain APR genes is that many confer multiple resistances, are effective against different pathogens [57]. APR genes are perfect targets for MAS because they provide only a moderate level of resistance and show insufficient ability to withstand artificial infectious backgrounds [58]. The list of wheat APRs is compiled in Table **3**.

The most prominent wheat APR gene is *Lr34,* described in 1977 by Dyck [59], who later assigned it to chromosome 7D [78]. Further studies showed that this gene was located on arm 7DS [79]. The *Lr34* gene was found to coincide with the gene *Yr18* for moderate resistance to stripe rust [80, 81], the *Pm38* gene for powdery mildew resistance [82], *Bdv1* for tolerance to barley yellow dwarf virus [83], and the *Sr57* gene for race-nonspecific moderate resistance to stem rust [78]. The *Lr34* gene is associated with leaf tip necrosis (LTN) [84]. Moreover, the association of *Lr34* and LTN with resistance to spot blotch disease (QTL *QSb.bhu-7D*) caused by the necrotrophic fungus *B. sorokiniana* was revealed by Kumar *et al.* [85]. It should be noted that *Lr34* also provides seedling resistance to leaf rust at low temperatures [86, 87]. Krattinger *et al.* [60] performed physical and genetic mapping of the *Lr34/Yr18/Pm38 /Sr57/Bdv1* gene (*Lr34*) and revealed that it encodes a pleiotropic drug resistance-like ATP-binding cassette transporter. The nucleotide sequence of *Lr34* is 11805 bp in length, consisting of 24 exons [60]. The resistance and susceptibility alleles of the *Lr34* gene differ by a single nucleotide polymorphism in intron 4, a deletion in exon 11, and a single nucleotide polymorphism in exon 12 [60, 88]. Abscisic acid turned out to be the substrate of the ABC transporter encoded by *Lr34* [89]. Transformation with *Lr34* proved to be beneficial for durum wheat, but in barley, it induced rapid developmental leaf senescence [90, 91].

Table 3. Wheat APR genes and their products.

Gene	Chromosome Location	Characteristic of the Protein or the Gene	Refs.
Lr34/Yr18/Pm38/Sr57/Bdv1	7DS	Pleiotropic drug resistance-like (PDR-like) ATP-binding cassette (ABC) transporter	[59, 60]
Lr22a	2DS	CC-NB-LRR	[61]
Lr46/Yr29/Pm39/Sr58	1BL	-	[62]
Lr67/Yr46/Sr55/Pm46	4DL	Hexose transporter	[63, 64]
Lr68	3BS	-	[65]
Lr74	3BS	-	[66]
Lr75	1BS	-	[67]
Lr77	3BL	-	[68]
Lr78	3DS	-	[69]
Yr36	6BS	Protein with a kinase and a putative START lipid-binding domain, HTAP	[70, 71]

(Table 3) contd.....

Yr52	7BL	HTAP	[72]
Yr59	7BL	HTAP	[73]
Yr62	4BL	HTAP	[74]
Yr78	6BS	-	[75]
Yr80	3BL	-	[76]
Sr2/*Lr27*/*Yr30*	3BS	-	[77]

The most pronounced level of APR against leaf rust is provided by the *Lr22a* gene from *Aegilops tauschii* Coss. on chromosome 2DS [92, 93], which accounts for the increased latent period and reduced sporulation but not a reduction in the number of pustules per unit area. The gene was cloned and turned out to be 2,739 bp in length, consisting of a single exon and coding for a 912-amino acid NLR protein of the CC type [61]. However, the Lr22a protein showed only low sequence homology to other cloned wheat NLRs, and its closest homolog in *Arabidopsis* is RPM1 conferring resistance to the bacterial pathogen *P. syringae* expressing either avrRpm1 or avrB. RPM1 is a peripheral membrane protein residing on the cytoplasmic surface of the plasma membrane. Its activation leads to hypersensitive response and growth restriction of *P. syringae* strains expressing AvrRpm1 or AvrB [94, 95].

Another APR gene, *Lr46/Yr29/Pm39/Sr58/Ltn2,* confers partial resistance to many biotrophic pathogens and is also associated with LTN [62, 96, 97]. The gene was localized in the distal region of chromosome arm 1BL and shown to confer the same type of resistance as *Lr34/Yr18/Pm38/Sr57/Bdv1* but at a lower level [98].

The *Lr67/Yr46/Sr55/Pm46/Ltn3* APR gene originated from accession PI250413 [99] and was transferred onto chromosome 4DL of the cultivar Thatcher producing line RL6077 [63]. No yield penalty is associated with the resistance allele of *Lr67* [63]. It confers partial resistance to all three wheat rust pathogens and powdery mildew and is also associated with LTN [100]. The *Lr67* gene was found to encode a hexose transporter that differs from the susceptible form by two amino acids and alters hexose transport [64]. The *Lr68/Ltn4* gene on chromosome 3BS is another APR conferring resistance against leaf rust only; it was first described in the spring bread wheat Parula and probably originated from the cultivar Fontana [65]. Other broad-spectrum leaf rust APRs were further identified in wheat: *Lr74* on chromosome 3BS of the cultivar Caldwell [66], *Lr75* on 1BS of the cultivar Forno [67], *Lr77* on chromosome 3BL of the cultivar Santa Fe [68], and *Lr78* on 3DS of the cultivar Toropi [69].

The *Yr36* gene conferring moderate APR against only stripe rust was introgressed from emmer wheat *Triticum dicoccum* Schrank ex Schübl. onto chromosome 6BS [70]. The gene is temperature-dependent (the resistance is expressed under higher temperatures) and encodes a protein with a kinase domain and a putative START lipid-binding domain being essential for the resistance [71]. Several other high-temperature adult-plant (HTAP) resistance genes such as *Yr52* [72] and *Yr59* on 7BL [73], *Yr62* on 4BL [74], as well as APRs *Yr78* on 6BS [75] and *Yr80* [76] on 3BL, have been identified but their presence in many cultivars over the world is questionable. The *Yr15* gene showing broad-spectrum all-stage resistance to stripe rust races was also transferred to bread wheat from emmer wheat. It is located on 1BS and encodes a kinase-pseudokinase protein designated as wheat tandem kinase 1 [101].

One of the most widely used broad-spectrum stem rust genes is *Sr2* [102], transferred from the emmer wheat cultivar Yaroslav in the 1920s to produce the cultivar Hope [103]. The *Sr2* gene is moderately effective against all races of stem rust, including the group of Ug99 races, although its expression in the field is often suppressed [104, 105]. *Sr2* was localized on chromosome 3BS [104, 106]. It is also pleiotropic with the juvenile race-specific leaf rust resistance gene *Lr27* as well as with partial resistance to powdery mildew and stripe rust (as *Yr30*) [77]. Surprisingly, *Sr2*-mediated resistance to stem rust and powdery mildew turned out to be associated with the death of photosynthetic cells around the infection site, similarly to hypersensitive response-type necrosis [107], although no NLR genes reside at the *Sr2* locus [108].

Among all-stage resistance genes, an interesting case is the stem rust *Sr26* gene, which retained its durability despite its deployment in a number of Australian cultivars since 1971 [109]. *Sr26* was introgressed from *Thinopyrum ponticum* (Podp.) Z. –W. Liu & R. –C. Wang as the T6AS.6AL-6Ae#1 translocation and proved to be an NLR of the CNL type; the same expectations are for another *Th. ponticum* gene, *Sr61*, which also encodes a CNL [109]. The gene *Sr62* from the wild diploid wheat relative *Aegilops sharonensis* Eig, which encodes a non-NLR protein (a tandem protein kinase) and provides broad stem rust resistance, is also promising [110]. However, not all such tandem kinase R proteins provide broad resistance. For example, the *Triticum monococcum* L. gene *Sr 60* encoding a tandem kinase (wheat tandem kinase 2) proved to be only race-specific [111].

Moreover, interactions between the broad-spectrum resistance genes such as *Sr2/Yr30*, *Lr34/Yr18/Sr57* and *Lr68* were shown to confer enhanced adult plant resistance to rust diseases in some bread wheat genotypes [112]. To provide broad-spectrum resistance to stem rust employing all-stage resistance genes (NLR genes), a transgenic approach was used by introducing a transgene cassette of five resistance genes into bread wheat (*Sr45, Sr55, Sr50, Sr35*, and *Sr22*) as a single locus [113]. However, it is still possible that new races with virulence to most of those *Sr* genes might appear [41].

In barley, there are three genes conferring APR to the leaf rust pathogen *P. hordei Rph20, Rph24*, and *Rph2*3 (Table **4**) conferring high, moderate, and low levels of APR, respectively, of which *Rph20* and *Rph24* are objects of MAS [114].

Table 4. Durable resistance genes against biotrophic pathogens in barley.

Gene	Chromosome Location	Characteristic of the Protein or the Gene	Refs.
Rph20	5H	leaf rust APR	[114]
Rph24	6H	leaf rust APR	[114]
Rph2 3	7H	leaf rust APR	[114]
mlo	4HL	recessive loss-of-function alleles of the gene encoding a plasma membrane-localized protein with seven transmembrane domains	[115]
Rbgh1	5HL	powdery mildew APR	[116]
Rbgh2	7HS	powdery mildew APR	[116]
Rbgh3	1HS	powdery mildew APR	[116]

The most prominent durable resistance source employed in barley breeding is the race-nonspecific powdery mildew resistance gene *mlo*, which is a recessive loss-of-function allele of the corresponding dominant allele *Mlo* [117, 118]. *Mlo* encodes a plasma membrane-localized protein with seven transmembrane domains, in which the N-terminus is located extracellularly and the C-terminus intracellularly [115, 119]. Among more than 40 *mlo* mutant alleles, only two (natural *mlo11* from Ethiopian accessions and induced mutant *mlo9*) have been involved in spring barley cultivars since 1979, providing powdery mildew immunity [117, 118]. Upon infection, barley *mlo* genotypes usually show the arrest of fungal pathogenesis at early stages, without the formation of haustoria and secondary hyphae. Local cell-wall callose appositions in host epidermal cells beneath attempted fungal penetration sites are formed accompanied by accumulation of defense-associated compounds, including hydrogen peroxide resulting in localized cell death and formation of necrotic leaf spots [118, 120]. In addition, the host genetic background determines the efficiency of *mlo* resistance [118, 120]. At the same time, the presence of *mlo* is considered to be associated with reduced resistance to some pathogens with necrotrophic developmental stages, such as enhanced sensitivity to *B. sorokiniana* toxins in comparison with nonmutant genotypes of barley [121], higher susceptibility to *Magnaporthe oryzae* [122], and *Ramularia collo-cygni* causing Ramularia leaf spot, which became a major barley disease in Europe [123]. In a series of *mlo* mutant plants of bread wheat produced by TALEN (transcription-activator-like nuclease) and TILLING (targeted induced local lesions in genomes) methods, the stronger powdery mildew resistance was also shown to be correlated with enhanced susceptibility to *M. oryzae* pathotype *Triticum* [124].

Three new APR genes (*Rbgh1, Rbgh2,* and *Rbgh3*) for powdery mildew resistance have been recently identified in barley landraces (Eth069 from Azerbaijan and HOR3270 from Turkey) in the terminal regions of chromosomes 5HL, 7HS, and 1HS, respectively [116]. As opposed to *mlo*, the presence of those genes was not associated with spontaneous necrosis and mesophyll cell death, and resistance was localized to the site of the attempted penetration of the fungus and cytologically involved cell wall appositions and cytosolic vesicle-like bodies, without strong induction of reactive oxygen species. One may expect that such powdery mildew APRs would not be associated with higher susceptibility to necrotrophic pathogens.

Factors of resistance against necrotrophic fungi of the genus Fusarium are considered to be quantitative, *i.e*., their additive effect providing the measured level of resistance in comparison with the plants lacking such factors [125]. Fusarium head blight (FHB), caused predominantly by *Fusarium graminearum,* is one of the most devastating diseases accompanied by the production of mycotoxins, which are harmful to humans and animals. The most effective and durable gene for FHB resistance by type II (resistance against symptom spread in the head) is *Fhb1* on chromosome 3BS. This gene was first described in the Chinese cultivar Sumai 3 developed in 1972 [126]. The *Fhb1* gene encodes the histidine-rich calcium-binding-protein (His), and the resistance allele resulted from a 752-bp deletion involving exon 3, leading to the change of the translation start codon [127, 128]. The deduced resistance variant of His is 14 residues longer than the wild-type protein and differs by 21 N-terminal amino acid residues [127]. This nucleus-localized protein is presumed to be involved in calcium signaling [127]. On the other hand, the FHB-resistant variety Sumai 3 shows a Fusarium seedling blight-susceptible reaction (resistance inversion) [129]. Apart from *Fhb1*, there are a number of other FHB resistance genes, including *Fhb7* introgressed from *Th. elongatum*, which encodes glutathione S-transferase and acts *via* detoxifying trichothecenes [130], as well as the susceptibility factor on 4DS [131], which could be targets of MAS for pyramiding resistance genes.

An important role in the regulation of plant interaction with pathogens belongs to the *NPR1* gene [132]. It was shown that in *A. thaliana,* the functional product of the gene plays a key role in the PR1 gene expression and switching between jasmonate-dependent and salicylate-dependent defense response [133]. Diethelm *et al*. [134] detected that certain alleles of homoeologous NPR1-like genes on wheat chromosomes 2D and 2A (*TDF_076_2D* and *TDF_076_2A*) conferred type II resistance to *F. graminearum* and *F. culmorum* at the level of 14.2% and 3%, respectively. Transformation of FHB-susceptible wheat cultivars with either *Arabidopsis* or *Secale cereale NPR1* genes led to improvement of FHB resistance [135, 136]. However, transferring the *NPR1* gene from *A. thaliana* into wheat caused increased susceptibility to *Fusarium asiaticum* at the juvenile stage, while in adult plants, on the contrary, it conferred resistance [137]. At the same time, knocking out *NPR1* genes (*Ta7ANPR1*) on homoeologous group 7 chromosomes in wheat increased resistance to stem rust [138]. Similarly, RNAi (RNA interference)-mediated stable silencing of the gene *TaCSN5*

(for constitutive photomorphogenesis 9 (COP9) signalosome – a regulator of plant growth and development) conferred broad-spectrum resistance to the stripe rust pathogen, which indicated that *TaCSN5* as a candidate susceptibility gene could be the object of genome editing for providing stripe rust resistant genotypes [139].

2.2. Advances in Virus Resistance Due to Biotechnological Approaches

Genetically modified plants produced *via* transgene-based host-induced gene silencing (HIGS) based on RNAi is a promising biotechnological approach to increase resistance to various pathogens, including viruses, fungi, and nematodes [140, 141]. RNAi silencing has been demonstrated to be especially effective for producing genotypes with virus resistance. For example, wheat plants transformed with a construct involving the sequence of a portion of the coat protein of wheat streak mosaic virus (WSMV) proved to be WSMV resistant [142]. Transformation of wheat plants with a polycistronic amiRNA (artificial microRNA) construct targeting various conserved regions in the WSMV genome resulted in WSMW immunity [143]. Similarly, barley plants transformed with a polycistronic amiRNA precursor construct based on the conservative sequence elements of several wheat dwarf virus (WDV) strains expressing three amiRNAs simultaneously resulted in highly efficient resistance to WDV [144]. Moreover, RNAi silencing of the endogenous wheat genes *TaeIF(iso)4E* and *TaeIF4G* encoding initiation factors induced resistance to WSMV, Triticum mosaic virus, soil-borne wheat mosaic virus and a significant reduction in barley yellow dwarf virus infection [145]. Further development of this approach led to the strategy of spray-induced gene silencing (SIGS) based on spraying double-stranded RNAs (dsRNAs) and small RNAs (sRNAs) targeting essential pathogen genes on plant surfaces, which does not require genetic modification of plants [141, 146].

Thus, durable resistance to fungal biotrophic pathogens in wheat and barley could be conferred by APRs. However, they provide only a moderate level of resistance and are to be supplemented by qualitative R genes with major effects. Silencing of susceptibility alleles, common for providing resistance to necrotrophs [23], or certain regulatory genes *via* mutagenesis or biotechnological approaches proved to be another way to increase resistance to biotrophic pathogens as well [118, 138, 139]. There are cases when the presence of some resistance factors to a certain pathogen may be associated with susceptibility to other pathogens [118] or increased susceptibility at juvenile stages [129, 137], which indicates their involvement in a complex regulatory network. In addition, HIGS based on RNAi is considered to be a promising universal approach for increasing resistance to various pathogens in crop species.

3. RICE

Among multiple diseases of rice, the most destructive and widespread are blast caused by the hemibiotrophic fungus *M. oryzae* (*Pyricularia oryzae*) and bacterial blight caused by *Xanthomonas oryzae* pv. *oryza* e (*Xoo*), a biotrophic bacterium [147, 148] (Table **5**). In this part, the main genes conferring durable resistance to primarily these diseases are reviewed as well as some biotechnological approaches to improve resistance are mentioned.

3.1. Durable Resistance against the Fungus *M. oryzae*

As *M. oryzae* is a fungus with the biotrophic phase of development, R genes providing complete resistance to blast are commonly defeated in 1-7 years after the release of resistant varieties [150]. Because of this, genes conferring broad-spectrum resistance are highly valuable. The most prominent gene for durable blast resistance in rice is the race-nonspecific recessive resistance gene *pi21* identified in the Japanese upland variety Owarihatamochi on chromosome 4 [151] (Table **6**). The wild-type susceptibility allele encodes a proline-rich protein with a putative heavy metal-binding domain and putative protein-protein interaction (proline-rich) motifs. The recessive resistance allele is a result of a loss-of-function mutation due to the deletion of the 18- and 48-bp sequences in the proline-rich region containing PxxPxxP, which is a “core motif” for protein-protein interaction [152]. It is assumed that *pi21* plays a role in the pre-penetration plant-pathogen interaction through elicitor-triggered immunity and ethylene signaling [150].

Another durable broad-spectrum resistance gene, *Ptr*, was identified in the resistant tropical *japonica* variety Katy on chromosome 12. This gene encodes an untypical resistance protein with four Armadillo repeats, which may represent a non-typical E3 ligase [153]. However, E3 ligase activity *in vitro* was not detected, so the authors assumed that the Ptr protein is more likely involved in protein-protein interactions. The *Ptr* gene is expressed constitutively and codes for two isoforms localized mainly in the cytoplasm. *Ptr* is also required for broad-spectrum blast resistance conferred by the NLR genes *Pi-ta* and *Pi-ta2* [153].

Table 5. Yield losses caused by main diseases in rice.

Disease	Yield Losses, %	Refs.
Blast	up to 60	[148]
Bacterial blight	up to 70	[148]
Rice stripe virus	up to 40	[149]

Table 6. Durable resistance genes against *M. oryzae* and *Xoo* in rice.

Pathogen	Gene	Chromosome Location	Characteristic of the Protein or the Gene	Refs.
M. oryzae	*pi21*	4	A recessive loss-of-function allele of the gene encoding a proline-rich protein with a putative heavy metal-binding domain and putative protein-protein interaction (proline-rich) motifs	[152]
	Ptr	12	a protein with four Armadillo repeats	[153]
	Pi35	1	NB-LRR	[154]
	Pi63	4	NB-LRR	[155]
	Pb1	11	APR, atypical CC–NB–LRR,	[156]
	PigmR	6	NB-LRR	[157]
Xoo	*Xa4*	11	cell wall-associated kinase	[158]
	Xa21	11	APR, LRR receptor kinase-like protein	[159]
	Xa3 (*Xa26*)	11	APR, LRR receptor kinase-like protein	[160]
	xa13	8	recessive gene encoding a putative sugar transporter with alterations in the promoter region	[161]
	Xa7	6	executor R gene encoding a protein of 113 amino acid residues	[162]

It should be noted that many broad-spectrum quantitative blast resistance genes turned out to be NB-LRR proteins with certain peculiarities in their structure or expression. The dominant race-nonspecific gene *Pi35* on chromosome 1 from the Japanese breeding line Hokkai 188, which retains its effectiveness for 60 years, is a typical R gene encoding an NB-LRR protein bearing multiple functional polymorphisms with respect to the race-specific allele *Pish* [154]. *Pi35*+ *pi21* was detected to be the most effective combination for the suppression of leaf blast [163]. In the Japanese upland rice variety Kahei, the major blast resistance QTL Pikahei-1(t) on chromosome 4 involves the gene *Pi63* encoding a typical NB-LRR protein, which differs from its susceptibility variant not only in amino acid sequence but also by the higher expression level [155]. The durable panicle blast 1 (*Pb1*) gene derived from the *indica* variety Modan shows adult panicle blast resistance, which has remained effective for about 40 years: it does not provide resistance at young vegetative stages, but the resistance level increases with plant growth and is retained even after heading [164]. This gene encodes an atypical CC–NB–LRR protein in whose NB domain the P-loop is absent and some motifs are degenerated; *Pb1* expression increases during the development [156]. It was further detected that *Pb1* resistance was negatively dependent on three QTLs located on chromosomes 7, 9 and 11 and positively dependent on one QTL on chromosome 8 [165]. The broad-spectrum resistance gene *Pi39* derives from the Chinese cultivar Haonaihuan [166]. Based on the *Pi39* candidate cDNA sequences, an InDel-based marker for *Pi39* gene selection was developed [167]. An interesting case of durable resistance to *M. oryzae* is the Chinese rice variety Gumei 4, which has been employed as a blast resistance donor for more than 50 years. This variety carries the *Pigm* resistance locus containing a cluster of NLR genes, among which *PigmR* confers broad-spectrum resistance, and *PigmS* competitively attenuates *PigmR* homodimerization to suppress *PigmR*-mediated resistance. It turned out that epigenetic regulation of *PigmS* fine-tunes disease resistance; *PigmS* increases yield by increasing seed setting and so counteracts yield penalties induced by *PigmR* [157].

Using sodium azide as a mutagen, the mutant line SA0169 showing broad-spectrum blast resistance was produced from the blast-susceptible Taiwan *japonica* cultivar Tainung 67. This mutant line retains its broad-spectrum blast resistance for about 20 years. The combination of two regions was detected to confer blast resistance in this mutant: a 1.16-Mb region on chromosome 6 (Pi169-6(t)) and a 2.37-Mb region on chromosome 11 (Pi169-11(t)) involving 2 and 7 candidate R genes in those regions, respectively [168].

Thus, in the rice gene pool, several genes provide durable broad-spectrum resistance to blast, which can be extended by mutagenesis and its new version, genome editing, or by genetic transformation with foreign resistance genes. For example, rice blast resistance was improved *via* CRISPR/Cas9-targeted knockout of the ERF (ethylene responsive factor) transcription factor gene *OsERF922* in the *japonica* rice variety Kuiku131, and the silencing did not affect agronomic traits [169]. Transgenic rice plants of the *japonica* rice cultivar Nipponbare expressing the wheat *Lr34* gene showed improved resistance against multiple isolates of *M. oryzae* [170].

3.2. Durable Resistance against the Bacterium *Xoo*

Bacterial blight caused by *Xoo* is also a highly damaging disease in rice (Table **5**). Currently, more than 40 *Xoo* R genes have been described, some of which are broad-spectrum ones and some provide only race-specific resistance, which nevertheless proved to be rather durable [171]. For example, the race-specific gene *Xa4* has been conferring durable *Xoo* resistance since the early 1970s. This gene encodes a cell wall-associated kinase; moreover, it strengthens the cell wall by promoting cellulose synthesis and suppressing cell wall loosening, thus increasing the mechanical strength of the culm and improving lodging resistance [158] (Table **6**). The *Xa21* gene, which encodes a leucine-rich repeat receptor kinase-like protein, is a broad-spectrum resistance gene derived from *O. longistaminata* [159]. *Xa21* expression increases with age providing full resistance only in adult plants, but overexpression of this gene in transgenic rice plants provides resistance at both seedling and adult stages [172]. The *Xa3* (*Xa26*) gene also encodes a protein of the LRR receptor kinase type; its expression also gradually increases from the early seedling stage to the adult stage. It shows a higher expression level in the background of the *japonica* rice, which results in

enhanced expression of defense-responsive genes, ultimately providing a higher level and spectrum of *Xoo* resistance as compared to the *indica* rice [160]. Overexpression of *Xa3* in transgenic rice plants enhanced resistance in both *indica* and *japonica* backgrounds [160].

The *Xa13* susceptibility gene belongs to the SWEET (Sugars Will Eventually be Exported Transporter) family encoding putative sugar transporters induced by transcription activator-like (TAL) effectors of *Xoo* [173]. Among others, this family includes such susceptibility genes as *OsSWEET11, OsSWEET12, OsSWEET13, OsSWEET14,* and *OsSWEET15* [174]. The resistance protein encoded by the recessive resistance allele *xa13* differs from the susceptibility variant by only one amino acid but resistance is provided *via* expressional non-reaction of *xa13* to *Xoo* infection due to alterations in the promoter region [161]. The promoter region of *Xa13* contains an upregulated transcription activator-like 1 (UPT) effector box, which is involved in the activation of expression by *Xoo* race 6 (PXO99). The induction of site-specific mutations into the UPT box using CRISPR/Cas12a technology to hinder TAL protein binding and gene activation resulted in the production of the genome-edited rice with improved bacterial blight resistance [175].

The *Xa7* gene confers bacterial blight resistance for more than 10 years and, importantly, remains effective at high temperatures and drought. It turned out to be a small orphan gene encoding a protein of only 113 amino acid residues, which is distinct from any other resistance proteins [162]. The XA7 protein is anchored in the endoplasmic reticulum membrane and induces programmed cell death. The *Xa7* promoter contains the 27-bp effector binding element, which is essential for AvrXa7-inducing expression [162]. According to Luo *et al*. [176], *Xa7* belongs to executor R genes and acts as a guard against pathogen's exploitation of the rice major susceptibility gene *SWEET14*. Lines with broad-spectrum *Xoo* resistance were produced by CRISPR/Cas9 technology *via* the generation of InDels in the TAL effector-binding element of the promoter of *OsSWEET* genes involved in disease susceptibility in rice plants [177].

Despite advances in the production of resistant forms *via* genetic transformation and genome editing, pyramiding *Xoo* R genes with resistance to different races using MAS remains an important approach to provide durable broad-spectrum resistance to bacterial blight of rice [148, 166, 178].

3.3. Durable Virus Resistance

In the context of resistance durability, the *Stvb-i* gene providing durable resistance to rice stripe virus (RSV), an RNA virus causative of rice stripe disease, should be mentioned. This gene encodes a 1,649-amino acid protein that lacks a NB-LRR domain but possesses a domain homologous to the histidine kinase/HSP90-like ATPase superfamily protein and is expressed mainly in meristematic tissues. It was suggested that *Stvb-i* may be involved in the protection of the meristematic tissue not only from RSV multiplication but also from heat stress [179], which is of importance in connection with global warming.

Thus, in rice, like in wheat, most cloned durable resistance genes against *Xoo* and *M. oryzae* are distinct from NLRs or, in the case of the latter pathogen, some encode untypical NB-LRR proteins or show peculiarities in their expression. Likewise, silencing of some susceptibility genes also improves resistance [164, 171, 173, 174, 177]. However, a unique case of achieving resistance to a number of different pathogens has been reported [180, 181]. Transgenic rice lines overexpressing the rice *BSR1* (BROAD-SPECTRUM RESISTANCE 1) gene, which encodes a putative receptor-like cytoplasmic kinase, turned out to be highly resistant to *Xoo* and *M. oryzae* [180]. In addition, they showed resistance to the bacterium *Burkholderia glumae,* which causes bacterial seedling rot and bacterial grain rot, as well as to the necrotrophic fungus *Cochliobolus miyabeanus,* causing brown spot [181]. Moreover, rice plants with *BSR1* overexpression showed slight resistance even to RSV [181]. Thus, overexpression of one gene, *BSR1*, is a unique and promising case as it could confer resistance to multiple diseases caused by pathogens of different trophic classes: biotrophs, hemibiotrophs and necrotrophs.

4. POTATO

Potato (*Solanum tuberosum* L.), the third most important food crop, is threatened by many different pathogens: bacteria, fungi, oomycetes, viruses, viroids, nematodes, and phytoplasmas, which affect both crop yield and quality. Moreover, because of the vegetative propagation of potatoes, pathogens could be transmitted *via* tubers to subsequent generations. This review focuses on advances in durable resistance to late blight caused by the oomycete *Phytophthora infestans* and to the economically important viruses, which cause high yield losses (Table **7**).

4.1. Approaches to Provide Durable Resistance to the Oomycete *P. infestans*

Late blight caused by the hemibiotrophic oomycete *P. infestans* is one of the most devastating diseases of potatoes. The pathogen rapidly overcomes R genes, so approaches to achieve durable resistance include deployment of quantitative resistance genes or multiple R genes simultaneously [184, 185]. The potato cultivar Sarpo Mira showed resistance to late blight for more than a decade after its release [186]. This cultivar was detected to carry the qualitative R genes *R3a, R3b, R4,* and *Rpi-Smira1,* as well as the quantitative resistance gene designated *Rpi-Smira2*, which confers partial field resistance [187]. However, later it was demonstrated that the *Rpi-Smira2* gene is located at the same position as the *R8* gene from the wild potato species *S. demissum* on chromosome 9 and both show recognition of the AVR8 effector, implying that *R8* and *Rpi-Smira2* are allelic [188]. *R8* encodes a typical NLR protein of the CC type (CNL) with 89% homology to *Sw-5*, tomato spotted wilt virus resistance R protein [188] (Table **8**). The *R8* gene was also shown to coincide with the previously identified QTL *dPI09c* for late blight resistance on potato chromosome 9 [189, 190], indicating that a single major disease resistance gene can be responsible for the QTL providing durable resistance.

Table 7. Yield losses caused by main diseases in potatoes.

Disease	Yield Losses, %	Refs.
Late blight	30-75, up to 100	[182]
Potato virus Y	59.6–77.9	[183]
Potato virus X	25.9–48.6	[183]
Potato leafroll virus	50.2–68.7	[183]

Table 8. Disease resistance genes employed for attaining durable resistance to *P. infestans*, PVY, and PVX in cultivated potato.

Pathogen	Gene	Chromosome Location	Origin	Characteristic of the Protein or the Gene	Refs.
P. infestans	*R8 (Rpi-Smira2)*	9	*S. demissum*	CC–NB–LRR	[188 - 190]
	Rpi-vnt1.1	9, cisgene	*S. venturii*	CC-NB-LRR	[191 - 193]
	Rpi-sto1	8, cisgene	*S. stoloniferum*	CC-NB-LRR	[191, 192]
	Rpi-blb1	8, cisgene	*S. bulbocastanum*	CC-NB-LRR	[192 - 194]
	Rpi-blb2	6, cisgene	*S. bulbocastanum*	CC-NB-LRR	[192, 193]
	Rpi-chc1	10, cisgene	*S. chacoense*	CC-NB-LRR	[192]
	Rpi-blb3	4	*S. bulbocastanum*	CC-NB-LRR	[195]
	Rpi-amr1	11	*S. americanum*	NRC helper-dependent CC-NB-LRR protein	[196]
	ELR	12, cisgene	*S. microdontum*	receptor-like protein ELR (elicitin response)	[197]
	StDMR6-1		*S. tuberosum*	loss-of-function mutation of the susceptibility gene encoding salicylic acid 5-hydroxylase	[198]
	StCHL1		*S. tuberosum*	loss-of-function mutation of the susceptibility gene encoding a transcription factor involved in brassinosteroid hormone signalling,	[198]
PVY	Ry_{adg}	11	*S. tuberosum* ssp. *andigena*	ER gene	[199]
	Ry_{chc}	9	*S. chacoense*	ER gene	[199]
	Ry_{sto} ($Ry\text{-}f_{sto}$)	12	*S. stoloniferum*	ER gene, TIR-NB-LRR	[200]
	$Ry(o)_{phu}$	9	*S. tuberosum* Group Phureja	ER gene	[201]
PVX	*Rx1* (*Rx*)	12	*S. tuberosum* ssp . *andigena*	ER gene, CC-NB-LRR	[202]
	Rx2	5	*S. acaule*	ER gene	[203]
PLRV	Rlr_{etb}	4	*Solanum etuberosum*	dominant gene	[204, 205]
	Rl_{adg}	5	*S. tuberosum* ssp . *andigena*		[206, 207]

An effective biotechnological approach to combine R genes in the same genotype is cisgene stacking, *i.e*., the introduction of stacks of cloned R genes from crossable wild potato species to existing varieties by genetic modification technology [191, 192]. To achieve broad-spectrum resistance, stacks of two genes, *Rpi-vnt1.1* and *Rpi-sto1* from *S. venturii* and *S. stoloniferum* [191], or three genes, *Rpi-blb1* and *Rpi-blb2* from *S. bulbocastanum* and *Rpi-vnt1.1* [193] were introduced into potato varieties. Within the framework of the research project on Durable Resistance in potatoes against *Phytophthora* (DuRPh), four varieties were transformed with one to three R cisgenes aimed to attain durable resistance to late blight [192].

Non-transgenic biotechnological approaches for the transfer of R genes from crossable wild species include somatic hybridization of cultivated potato with a wild species and identification of resistance genes using gene-specific markers [194, 195]. For example, backcross clones of potatoes with broad-spectrum late blight resistance due to the introgressed resistance genes *Rpi-blb1* and *Rpi-blb3* from *S. bulbocastanum* were produced with those methods [195].

The potential of wild potato species as sources of new late blight resistance genes seems to be not fully studied, as resistant accessions were identified among several species that were never previously reported to be late blight resistant: *Solanum albornozii*, *S. agrimoniifolium*, *S. chomatophilum*, *S. ehrenbergii*, *S. hypacrarthrum*, *S. iopetalum*, *S. palustre*, *S. piurae*, *S. morelliforme*, *S. neocardenasii*, *S. trifidum*, and *S. stipuloideum* [208]. A new R gene, *Rpi-amr1,* from *S. americanum* encoding an NRC helper-dependent CC-NLR protein with broad-spectrum resistance representing a family of nine resistant alleles is promising for the transfer of broad-spectrum durable resistance against *P. infestans* to *S. tuberosum* [196]. Du *et al*. [197] cloned a gene for the receptor-like protein ELR (elicitin response) from *S. microdontum.* This protein is involved in extracellular recognition of the elicitin domain representing a conserved molecular pattern in *Phytophthora* species. Transformation of cultivated potatoes with the ELR gene resulted in enhanced resistance to *P. infestans* and the authors proposed to pyramid ELR with cytoplasmic NLRs to maximize the potential for disease resistance durability.

Genome editing technology could be effective for knocking out susceptibility genes in potatoes. Using a CRISPR/Cas9 system with co-expression of two guide RNAs, tetra-allelic deletion mutants with functional knockouts of the susceptibility genes *StDND1*, *StCHL1* and DMG400000582 (*StDMR6-1*) were generated, and the edited plants showed increased resistance against late blight [198]. Of them, the authors report *StDMR6-1* and *StCHL1* as promising S-gene targets for late blight resistance breeding as they do not affect plant growth phenotypes.

Analysis of QTLs may be helpful in identifying durable quantitative genes for late blight resistance. The study of the relationship of 65 candidate genes with late blight resistance QTLs in three diploid potato populations PCC1, BCT, and PD detected three significant cases: the locus of a putative receptor-like protein kinase b on chromosome 11, the *Lox* gene on chromosome 3 and two protein phosphatase loci in a QTL with the largest effect on chromosome 12 [209]. The association mapping study of *S. tuberosum* Group Phureja revealed two late blight resistance QTLs with the candidate genes encoding a potato homolog of thylakoid lumen 15 kDa protein (StTL15A) and a stem 28 kDa glycoprotein (StGP28) with the 7% and 11% effects, respectively [210]. Juyo Rojas *et al*. [211] identified 16 organ-specific QTLs conferring resistance to late blight, explaining 13.7% to 50.9% of the phenotypic variance. *In silico* analysis revealed that four candidate genes for resistance to late blight have no functional genome annotation (including those for QTLs with 50.9% and 38.4% effects), while eleven candidate genes encode diverse proteins, including a leucine-rich repeat kinase.

Many QTLs for late blight resistance were identified in the wild species *S. microdontum* and *S. pampasense* [212]. The effects of those QTLs ranged from 16.9 to 47.5%, and they can be employed for introgression into cultivated potatoes [212].

4.2. Advances in Virus Resistance

The greatest advances with respect to durable resistance of potatoes were achieved for virus resistance due to natural resistance genes as well as genetic transformation and genome editing. There are two main types of resistance against potato viruses: hypersensitive resistance (HR), which is a rapid defense response resulting in the programmed cell death (necrosis) at the site of infection, and extreme resistance (ER), which is characterized by the absence of symptoms and prevention of virus multiplication at the early stage of infection [199, 213, 214]. HR genes are strain-specific, whereas ER genes are effective against all strains of the virus.

Among potato viruses, potato virus Y (PVY) is the most economically serious [183, 215] (Table **7**), with wild species being the reservoir of many PVY resistance genes. HR against PVY is conferred by *Ny* genes, and ER is mediated by *Ry* genes [199]. The ER genes Ry_{adg}, Ry_{sto} and Ry_{chc}, which are employed in breeding programs, originate from *S. tuberosum* subsp. *andigena*, *S. stoloniferum,* and *S. chacoense*, respectively, and many PCR markers are available for MAS [199].

The extreme resistance gene Ry_{sto} on chromosome 12 encodes an NLR protein with an N-terminal TIR domain, which recognizes the PVY coat protein (Table **8**); Ry_{sto}-dependent extreme resistance is temperature-independent, requires EDS1 (Enhanced Disease Susceptibility 1) and NRG1 (N requirement gene 1 proteins), and is epistatic to *Ny-1*-mediated HR [200]. Another PVY extreme resistance gene derived from *S. stoloniferum*, $Ry\text{-}f_{sto}$, had been mapped on potato chromosome 12 [216]. Still, later $Ry\text{-}f_{sto}$ was considered as the allele of Ry_{sto}. The alignment of sequences of the Ry_{sto} and $Ry\text{-}f_{sto}$ alleles revealed their 100% sequence identity in the coding and non-coding regions of the 4.85 kb amplified product [200]. In addition, a new dominant PVY ER gene designated *Ry(o)phu* was mapped on chromosome 9 of *S. tuberosum* Group Phureja, which provides broad-spectrum PVY resistance to prevent the virus's systemic spread [201].

The *Rx1* gene (also referred to as *Rx*) for extreme resistance against potato virus X (PVX) controls an NLR protein of the CC type [202]. *Rx1* is located on chromosome 12 and derives from *S. tuberosum* subsp. *andigena*; another PVX ER gene, *Rx2* introgressed from *S. acaule*, is located on chromosome 5 [203]. *Rx*-mediated extreme resistance is also epistatic to N-mediated HR [202]. Recently a new partial PVX resistance phenotype was identified in the potato cultivar Waiyin-1 [217]. In Waiyin-1, the infection of PVX was delayed by five days compared with the susceptible cultivar Kexin-1. This partial resistance accounted for the inhibition of PVX replication but not cell-to-cell or long-distance movement of the virus [217].

Potato was among the first genetically modified plants with changed virus resistance. Transformation of the potato cultivar Russet Burbank with the coat protein genes of PVX and PVY conferred resistance to infection by PVX and PVY [218], as was later demonstrated due to RNAi. Similarly, 100% resistance to infection by either PVY or potato virus A (PVA) was achieved in transgenic potato plants of the cultivar Vales Sovereign expressing segments derived from the capsid protein coding sequences of PVY (PVY strain O) and the cylindrical inclusion body coding sequences of PVA [219]. Constitutive overexpression of the gene *StSAR1A* encoding a small GTP-binding protein enhanced the resistance of transgenic potato plants against PVY and PVA [220]. The authors suggest that such transgenic plants could have enhanced resistance or tolerance to multiple biotic and abiotic stresses. To target multiple PVY strains, Zhan *et al*. [221] designed sgRNAs (small guide RNAs) based on 100% complementarity to conserved regions in sequences for the viral proteins P3 (the potyviral membrane protein involved in virus replication, systemic infection, pathogenicity, and movement), CI (involved in the formation of the laminate cytoplasmic inclusion bodies, as well as virus movement and infection), NIb (the RNA-dependent RNA polymerase), and the coat protein. Transgenic potato lines expressing the Cas13a/sgRNA constructs showed suppression of PVY accumulation and disease symptoms and thus possessed broad-spectrum PVY resistance.

Potato leafroll virus (PLRV) is also among the most destructive viruses of potatoes (Table **7**). The gene Rlr_{etb} confers PLRV resistance due to reduced PLRV accumulation

in foliage and the inhibition of the systemic spread of PLRV from infected foliage to tubers. It was introgressed from the non-tuber-bearing wild potato species *S. etuberosum* [204, 205]. The Rl_{adg} gene conferring high resistance level and low accumulation of PLRV was derived from *S. tuberosum* ssp. *andigena* [206, 207]. QTL analysis of resistance to PLRV accumulation revealed the major QTL *PLRV.1* on potato chromosome 11, explaining 50–60% of the phenotypic variance, which can be traced using molecular markers [222, 223].

Expression of the full-length PLRV replicase gene in transgenic potato plants of the cultivar Russet Burbank provided a high level of field resistance to PLRV [224]. Marker-free transgenic PLRV-resistant plants were generated using an inverted repeat construct corresponding to a PLRV coat protein gene segment employing the heat inducible Cre-loxP system to excise the nptII antibiotic resistance marker gene [225]. Inhibition of expression of the gene for movement protein (MP) *via* RNAi was also proposed as a method for the production of PLRV-resistant plants, and, as MP homologues are present in most plant viruses, the authors suggested that this technology could be used for generating virus-resistant plants of other species [226].

Thus, in cultivated potatoes, late blight resistance is mostly based on pyramiding NLRs, primarily those from wild relatives, achieved mainly by MAS and genetic transformation of cloned genes, and the nature of this resistance does not show much promise as to their longevity. Currently, genome editing is used to improve late blight resistance by silencing susceptibility genes, which could potentially provide more durable resistance. At the same time, cloning of virus resistance genes showed that NLRs provide durable resistance against potato viruses. Reliable advances in virus resistance are also associated with transgenic plants.

CONCLUSION

Different mechanisms of plant resistance highly depend on the nutrition types of pathogens and may be quite ambiguous. Molecular markers proved to be of much help for traditional breeding of the main food crops to pyramid monogenic quantitative resistance genes involved in durable resistance and qualitative R genes, significantly reducing time and cost spent to obtain lines or cultivars with the genes of interest. More importantly, direct manipulations with genotypes are becoming more widely and successfully used for understanding the resistance and susceptibility mechanisms, as well as engineering crop genotypes with broad-spectrum durable resistance, employing both transgenesis and genome editing, primarily the CRISPR/Cas technologies. Durability of resistance is the main challenge in the case of biotrophic and hemibiotrophic fungi, oomycetes, and bacteria with high evolutionary potential. However, in wheat, barley, and rice, there are a number of broad-spectrum durable resistance genes to such specialist pathogens that are different from NLRs, in contrast to potato. Related species remain a source of promising broad-spectrum resistance genes against such diseases, especially in the case of potatoes. Traditional mutagenesis and novel gene-editing technologies are of importance for improving disease resistance, in particular, by the production of loss-of-function alleles. Silencing of some, often regulatory, genes or overexpression of some host genes, as well as the introduction of foreign genes, by genetic modification are promising biotechnological ways for the production of genotypes with durable broad-spectrum resistance.

LIST OF ABBREVIATIONS

ABC	=	ATP-binding cassette
amiRNA	=	Artificial microRNA
APR	=	Adult Plant Resistance
CC	=	Coil-Coiled
CNL	=	Coil-coiled-type NLR
CRISPR/Cas	=	clustered regularly interspaced short palindromic repeats/**C**RISPR **as**sociated protein
DAMP	=	Damage-Associated Molecular Pattern
dsRNA	=	double-stranded RNA
ELR	=	Elicitin Response
ER	=	Extreme Resistance
ETI	=	Effector-Triggered Immunity
FHB	=	Fusarium Head Blight
HIGS	=	Host-Induced Gene Silencing
HR	=	Hypersensitive Resistance
HTAP	=	High-Temperature Adult-Plant
IP	=	Invasion Pattern
LRR	=	Leucine-Rich Repeat
MAMP	=	Microbe-Associated Molecular Pattern
MAS	=	Marker Assisted Selection
MP	=	Movement Protein
NAMP	=	Nematode-Associated Molecular Pattern
NB	=	Nucleotide-Binding
NLR	=	Nucleotide-Binding Domain Leucine-Rich Repeat
NPR1	=	Nonexpressor of Pathogenesis-Related Genes 1
PAMP	=	Pathogen-Associated Molecular Pattern
PLRV	=	Potato Leafroll Virus
PVA	=	Potato Virus A
PVX	=	Potato Virus X
PVY	=	Potato Virus Y
PRR	=	Pattern Recognition Receptor
PTI	=	Pattern-Triggered Immunity
QTL	=	Quantitative Trait Locus
RNAi	=	RNA Interference
RSV	=	Rice Stripe Virus
SA	=	Salicylic Acid
sgRNA	=	Small Guide RNA
SIGS	=	Spray-Induced Gene Silencing
sRNA	=	Small RNA
SWEET	=	Sugars Will Eventually be Exported Transporter
TAL	=	Transcription Activator-Like

TILLING	=	Targeted Induced Local Lesions in Genomes
TIR	=	Toll/Interleukin-1 Receptor-like
TNL	=	Toll/interleukin-1 Receptor-like-type NLR
UPT	=	Upregulated By Transcription Activator-like 1
WDV	=	Wheat Dwarf Virus
WSMV	=	Wheat Streak Mosaic Virus
Xoo	=	*Xanthomonas oryzae* pv. *oryza*e

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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