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REVIEW ARTICLE

Unravelling the potential of susceptibility genes in plant disease management: Present status and future prospects

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Abstract

The increasing global population requires an equivalent increase in food production to meet the global food demand. Crop production is challenged by various biotic and abiotic stresses, which decrease crop yield and production. Thus, proper disease management for crops ensures global food security. Various chemical, physical, and biological disease control methods have been devised and used for plant protection. However, due to the low efficiency of these methods, modern research has shifted to genetic engineering approaches. The recent advances in molecular techniques have revealed the molecular mechanisms controlling the plant's innate immune system and plant-pathogen interactions. Earlier studies revealed that the pathogens utilize the susceptibility (S) genes in hosts for their sustainability and disease development. The resistance achieved by suppressing the S genes expression provides resistance against pathogens. Exploiting S genes for imparting/enhancing disease resistance would offer a more durable and effective alternative to conventional disease control methods. Therefore, the present review highlights the potential of this novel tool for inducing disease resistance in plants.

Keywords

Susceptibility; resistance; disease; silencing

Introduction

The global population is growing alarmingly, and improved crop varieties are required to ensure the increasing food demand. The efforts to increase crop production are often limited by various biotic and abiotic stresses (1, 2). Biotic stress due to microbial pathogens, insects, and weeds can decrease crop production by up to 40%, out of which about 15% of yield loss is caused only due to diseases (3, 4). Thus, proper disease management for crop protection is important for ensuring global food security.

Various physical, chemical, and biological disease control methods have been devised and used for plant protection. Crop rotation and the use of pesticides are the most common methods for disease management, but their efficacy is accompanied by undesired side effects, rendering their use (5, 6). These conventional methods are inefficient and are not eco-friendly. Moreover, traditional breeding approaches for developing resistant varieties are tedious and time-consuming. Therefore, researchers are trying to

develop alternative strategies using modern genetic engineering tools to induce resistance against diseases (7-9). These approaches enable the manipulation of the gene(s) of interest without affecting the rest of the genome in a short period. These approaches allow interspecific gene transfer and are also applicable to the crops that are multiplied vegetatively (10, 11). However, the knowledge of candidate gene(s) in hosts, and pathogens is the prerequisite for proper disease management using genetic engineering -based approaches.

Recently the research on plant-pathogen interactions revealed how host plants and pathogens co-exist through evolution. The host plant has a defense system to protect it against the pathogen, and the pathogen develops a counterattack to overcome the defense barrier. The knowledge about the defense pathway and pathogen's counterattack will help in the development of durable resistance (5, 12). Different pathogens (viruses, bacteria, nematodes, or filamentous microbes) interact in different ways with the host plant. Viruses enter plant cells mechanically or through a vector such as an insect, nematode, or fungus. Bacteria produce virulence biomolecules through type II, III, and IV secretion systems which interact with the host plant (13, 14). Filamentous pathogens release biomolecules into the plant apoplast and cytosol. Plants, when infected, can resist the pathogen through pathogen-associated molecular patterns (PAMPs) detected by pattern recognition receptors (PRRs), leading to PAMP-triggered immunity (PTI), which acts as the first line of defense. After a pathogen attack, the plant generates endogenous signals called damage-associated molecular patterns (DAMPs) to activate PTI. The pathogen develops its counterattack system and produces effector molecules to overcome the host immune system and induce effector-triggered susceptibility (ETS). These effectors activate the second line of defense in the host, which is referred to as effector-triggered immunity (ETI). Thus, it can be concluded that PTI, ETS, and ETI form the layers of the plant's innate immune system against pathogens (15-17). This knowledge of the plant-pathogen molecular interactions in disease protection and development can help in the production of resistant/less susceptible crops.

Susceptibility (S) genes present in plants are responsible for the susceptibility of plants to the pathogen. Pathogens took advantage of these susceptibility genes for their sustainability and disease development. However, with the advent of modern genetic engineering and genome editing technologies, these susceptibility genes could pave the way toward the development of multiple disease-resistant crop varieties by knocking out these S genes (18-20). The suppression of S genes can help in inducing resistance in plants against pathogens. For example, suppressing the powdery mildew resistance 6 (PMR6) gene restricted the development of powdery mildew in wheat (21). The functional knockouts of StDND1, StCHL1, and StDMR6 showed enhanced resistance against late blight in potatoes (19). The resistance achieved by suppressing the expression of S-gene(s) would provide durable resistance compared to R genes, as the former involves an important constituent required by the pathogen, which is less likely to change (20). The suppression or silencing of S-gene can be achieved through RNA-interference (RNAi) technique due to its greater and more diverse mode of action. It is a post-transcriptional regulation of genes through interception and degradation of mRNA. Using this strategy, it is possible to alter the susceptible gene(s) to induce enhanced expression of the defense pathway (22). Therefore, the present review highlights this novel tool for inducing disease resistance in plants, which can act as a boon for sustainable agriculture.

RNAi

RNA silencing is a conserved regulatory mechanism of gene expression. In fungi, it is called gene quelling, and in animals, it is referred to as RNA interference (RNAi). It takes place at the nucleotide level, in which a sequence-specific process accounts for the mRNA degradation or causes post-transcriptional gene silencing (PTGS) or interference at the transcriptional level via RNA-directed DNA methylation (RdDM). PTGS involves the inhibition of translation at the post-transcriptional level, and RdDM refers to the epigenetic modification achieved via methylation. It can inhibit the expression of candidate genes responsible for biotic and abiotic stresses (23, 24).

Various parts of basic RNA silencing machinery include a dsRNA, Dicer, or a Dicer-like (DCL) protein; small RNAs (21-24 nucleotides); an RNA-induced silencing complex (RISC). The dsRNA triggers the pathway, which is processed by DCL to give small RNAs. Double-stranded siRNAs get incorporated in the RNA-induced silencing complex (RISC). RISC complex consists of Dicer, ARGONAUTE, RNA binding protein (PDR), and transacting RNA-binding protein (TRBP). The siRNA duplex constitutes the guide strand and passenger strand. One out of two strands is removed while the other remains bound to the RISC (guide) and activates the complex (25, 26). The strand with weak interaction with the complementary strand remains attached while the strongly bonded strand is degraded. Activation of RISC is associated with an energy-consuming (ATP-dependent) unwinding of siRNA, which results in the formation of a guide strand. This guide strand is antisense in direction, then complementary base pairs with the mRNA sense strand and causes mRNA degradation (Fig. 1). Targeted mRNA degradation inhibits protein synthesis, thereby silencing the target gene.

The insight into RNA-mediated gene silencing led to the development of transgenic plants by exploiting the genome of the pathogen or host for disease management. Transgenic plants with improved traits can be produced by RNAi-based techniques such as virus-induced gene silencing (VIGS), host-induced gene silencing (HIGS), and RNAi hairpin construct. VIGS provides a rapid tool for validating gene functionality by silencing of the target gene (27, 28). HIGS is used for inducing resistance in plants by employing the pathogen gene (Avirulence) involved in disease establishment. Hairpin construct development for genes responsible for plant susceptibility or virulence in pathogens provides a tool for disease control.

RNAi has become a useful tool for studying gene function and has potential applications for treating plant diseases, including those related to susceptibility genes. Susceptibility genes make individuals more likely to develop certain diseases or conditions. RNAi can be used to study the function of susceptibility genes by knocking down their expression and observing the effects on cellular processes and disease development. For example, plants are susceptible to different viruses, which can cause significant damage to crops and reduce yields. RNAi has been used as a potential tool for developing resistant plants by targeting the viral genes or host susceptibility genes involved in the viral infection (29). In *Arabidopsis thaliana,* gene PENETRATION3 (PEN3) is involved in the susceptibility of plants to the bacterial pathogen *Pseudomonas syringae* (30). In this case, knocking down the expression of the PEN3 gene could make the plant more resistant to the pathogen. One study used RNAi to knock down the expression of the PEN3 gene and found that it reduced the plant's susceptibility to *P. syringae*. The researchers introduced double-stranded RNA (dsRNA) targeting the PEN3 gene into the plant cells, which triggered the RNAi pathway and

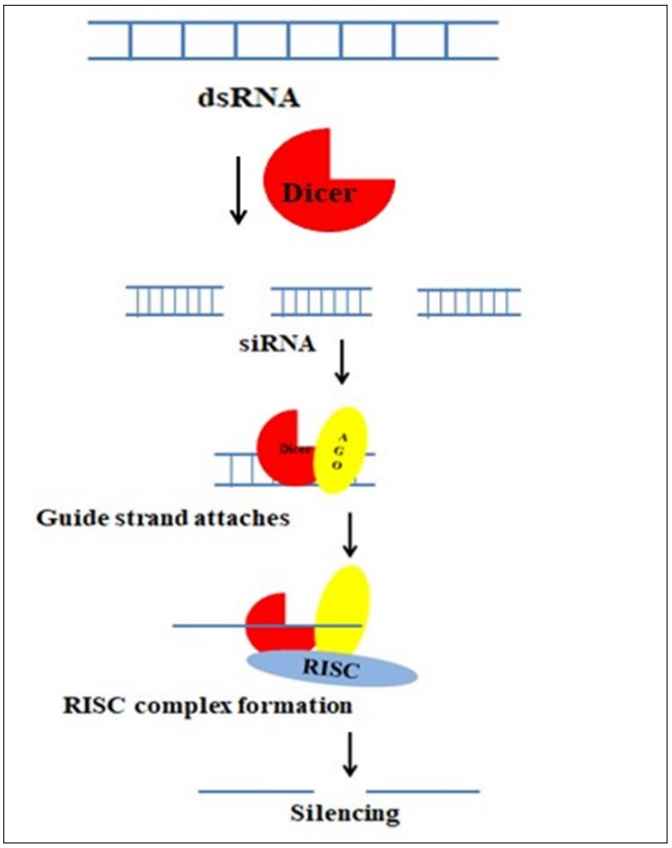

Fig. 1. Mechanism of RNAi mediated silencing

led to the degradation of PEN3 mRNA. The resulting knockdown of PEN3 expression led to a decrease in bacterial growth and an increase in plant resistance to infection (30). Overall, these studies demonstrated the potential for RNAi to be used to knock down susceptibility genes in plants and improve their resistance to diseases (29, 30).

Concept of resistance in plants

Plants can resist pathogen infection both extracellularly and intracellularly. Extracellular detection of pathogens is achieved through PAMPs such as bacterial flagellin and fungal chitin, which are conserved microbial elicitors. The receptor proteins in the plant plasma membrane that recognize PAMPs are called pattern recognition receptors (PRRs). This interaction of PAMPs with PRRs lead to resistance in host plants through PAMP-triggered immunity (PTI) (Fig. 2). PTI is related to the activation of various other pathways such as mitogen-activated protein kinase (MAPK) cascade, calcium influx, an oxidative burst, etc. (16, 31). However, the pathogens are also evolving themselves to surpass the extracellular detection by the host plants. Pathogens release effector molecules to suppress their detection and cause disease. This type of susceptibility in the host plant is called effector-triggered susceptibility (ETS). Effector molecules are the pathogen virulence molecules. The plant defense machinery is continuously co-evolving with the pathogen's attack. To protect the plants through ETS, plants develop intracellular receptors such as NLRs to detect effectors, leading to resistance through ETI. The ETI appears as a hypersensitive response (HR) associated with apoptosis at the infected site representing an enlarged version of the PTI response (32).

Recognition of the pathogen can induce defense responses like enhanced reactive oxygen species (ROS) and nitric oxide (NO) production through the activation of (Ca^{2+}), which acts as a secondary messenger. External stimulus like the production of H_2O_2 and effectors during stress in plant increases the Ca^{2+} concentration, which is detected by Ca^{2+} sensors and leads to phenomena such as hypersensitive response, production of H_2O_2, and NO. Thus, Ca^{2+} signaling plays an important role in PTI/ETI perception (33). Thus, the plant's innate immune system collectively includes PTI, ETS, and ETI to induce the disease resistance in plants. Susceptibility genes can be involved in either the PTI or ETI pathway, and their function can be targeted to improve plant resistance against pathogens. Knocking down susceptibility genes can enhance PTI or ETI responses, increasing resistance to pathogens (34).

Type of resistances

Disease resistance in plants can be categorized as qualitative and quantitative. Qualitative resistance is offered by R genes that utilize genes with large effects and are discontinuous in nature making them less durable and specific (35). This resistance conferred by the dominant genes is also referred to as prevalent resistance.

The resistance offered by the loss of S-genes is quantitative resistance, including genes with minor additive effects. Quantitative resistance is durable, polygenic, and horizontal (36, 37). The horizontal resistance being non-specific owes to its broad range of applicability (38). The S-gene(s) mediated resistance is also called recessive resistance. The pathogen requires host susceptibility factors for its establishment in the host (20, 39). When the interaction between susceptibility factors and the pathogen is incompatible, it leads to resistance in plants. As the susceptibility factors are dominant, the S-gene-mediated resistance, through its suppression/loss of function, needs all gene copies in a recessive state. Therefore, this type of resistance achieved by recessive genes is called recessive resistance (20, 33).

S-genes and their role in plant immunity

S genes have been classified into three categories based on the point at which they act. First-class of S-genes includes the genes involved in the early stages of infection and help in pathogen establishment. The second class consists of the genes which alter the host defense negatively. The third class includes genes that help to sustain the pathogen in the host (40) (Fig. 3).

S-genes and their role in plant immunity

This class of genes required by the pathogen for its establishment in the host belongs to the first-class S-genes. These genes are active during early infection stages, i.e., pre-penetration (40). The penetration of pathogens inside the host plant varies with different pathogens. Bacteria enter through stomata or lesions and utilize type III and type IV secretion systems for injecting effectors inside the host cell, which help in surpassing the plant immune system. Fungi and oomycetes penetrate through hyphae generated from spores. A developed haustorium can assist in feeding and transporting the effector for pathogen establishment (41). Various first-class S-genes involved in helping pathogens and establishing infection through various entry points have been studied and discussed as follows.

Entry through cuticle and cell wall structure

The plant leaf surface is waxy and consists of the cuticle, which constitutes cutin, wax, polysaccharides, and compounds such as flavonoids (42). The mutant glossy11 gene in corn showed decreased susceptibility to powdery mildew due to poor germination of spores as the amount of very-long-chain aldehyde levels reduced in leaf cuticles (43). Similarly, a *Medicago* mutant- ram2 with changed cutin composition resulted in decreased susceptibility to *Phytophthora palmivora* (44). An alteration with the wax composition in *Medicago* irg1 caused reduced susceptibility to fungal rust and *Phakopsora pachyrhizi*, *Puccinia emaculata*, and *Colletotrichum trifolii* (45). The altered cuticle in *Arabidopsis* provided resistance to *Botrytis* and *Sclerotinia*. The inactivation of enzymes such as fatty acid oxidase, fatty acid hydroxylase, and long-chain acyl CoA synthetase

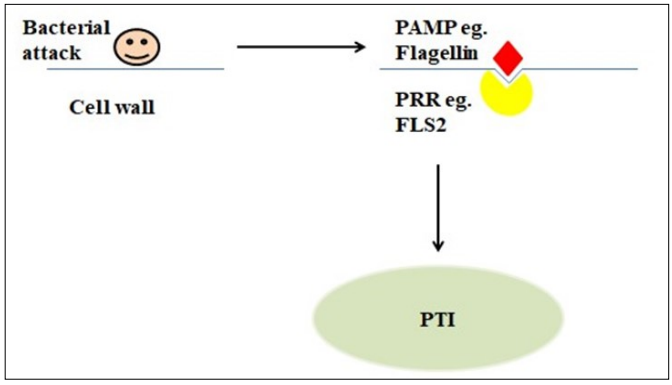

Fig 2. PAMP-triggered immunity

makes the cuticle more permeable, which enables the perception of elicitors to induce plant defense (46).

The plant cell wall and its composition help in the determination of plant-pathogen compatibility. Expansin present in the plant cell is responsible for the flexibility and growth of the cell wall. Expansin EXLA2 helps in the entry of pathogens and is important for susceptibility to *Botrytis* and *Alternaria* (47). Cell walls contain cellulose as the major structural component, and it was found that the Agrobacterium infection requires the cellulose synthase-like gene CSLA9 (rat4) for susceptibility. Alteration of csla9/rat4 showed reduced attachment of Agrobacterium to the root surface (48, 49).

Entry through stomata

Bacterial pathogens enter the host plant through wounds or natural openings, such as stomata or hydathodes, due to their inability to break the cell wall. The stomata close on the encounter of the pathogen to prevent the plant from infection and open afterward for the exchange of gas. The S-genes involved in stomatal closing (LecRK, AHA1, RIN4) are associated with increased susceptibility, and their suppression makes the entry of pathogens difficult, thereby decreasing susceptibility. Filamentous pathogens penetrate the cell wall to form specialized structures, which later help in providing nutrition. MLO (mildew resistance locus O) is the best-known susceptibility gene responsible for penetration in powdery mildew. MLO was first identified in barley and characterized as a membrane-anchored protein. Powdery mildew susceptibility owing to MLO has been reported in Arabidopsis, pea, tomato, pepper, wheat, and strawberry (40). A protein BAX inhibitor-1 (BI-1) with a similar potential for PM penetration in Barley has been reported (50, 51). BI-1 proteins belong to Lifeguard (LFG) proteins family (52). Other five LFG proteins identified in Arabidopsis and barley have also been reported for susceptibility. Studies have suggested the role of these proteins in suppressing defense responses or facilitating nutrient transfer (53). Cytoskeleton elements such as small G proteins (Rho-GTPases, or RAC/ROP) and GTPase activating proteins (GAP) have also been reported for pathogen susceptibility (54). HvRACB, HvRAC1, HvRAC3, and HvROP6 increase disease susceptibility (55, 56). It was observed that HvRAC1 provided resistance against *Magnaporthe oryzae*, indicating that the fate of genes is not fixed and depends on the pathogen (57). Susceptibility to *M. oryzae* in rice includes OsRAC4, OsRAC5, and OsRACB genes (58, 59). ARF-GAP protein (AGD5) of *Arabidopsis thaliana* acts as a susceptibility factor in *Hyaloperonospora arabidopsidis* infection (60). It can be concluded that these host S genes involved in (pre) penetration decide the aptness of the host plant, and therefore, the resistance provided by their suppression would induce a non-host type of resistance (40).

S-genes altering host defences

This type of S-genes codes for the genes which negatively regulate the plant defense system by interfering with defense responses such as PTI, salicylic acid signalling, and/or systemic acquired resistance (SAR). Examples are U-box E3 ubiquitin ligases (PUB22/23/24), enhanced disease resistance 2 (EDR2), and suppressor of npr1-1 inducible 1 (SNI1) (40). The plant defense system induces callose production when attacked by the pathogen, limiting the penetration by providing a physical barrier to entry. It was

proved that the overexpression of S-gene PMR4 led to callose accumulation and provided resistance against *Blumeria graminis* in *A. thaliana*. Pathogen counter-attacks the plant immunity and establishes infection by altering PTI or a component of a defense mechanism. PMR4 silenced mutant also provided resistance to *B. graminis*, and *H. arabidopsidis*. This indicates the susceptibility provided by PMR4 depends on some other factor that changes the expression of S-gene. In this case, the suppression of salicylic acid (SA) signaling led to an increase in the expression of the defense gene (61). A similar response was observed in IOS1 (impaired oomycete susceptibility) mutants where induction of PTI-responsive genes was delayed when infected by *H. arabidopsidis*, but an increase in their expression suggested its negative role in the activation of PTI through involvement in FLS2/BAK1 protein complex formation (62).

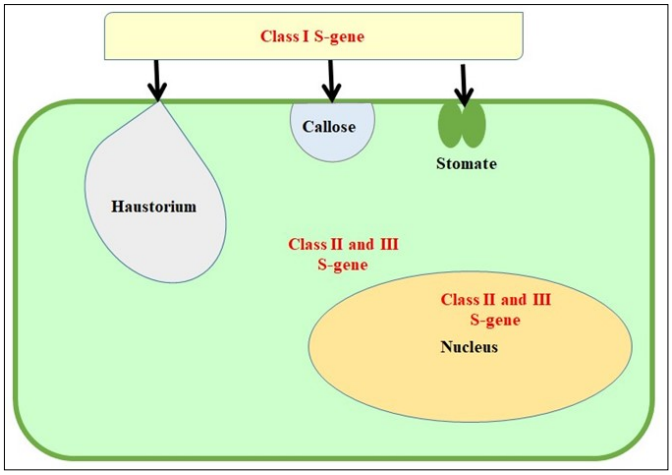

Fig 3. Type of S-genes involved in plant disease development

The mitogen-activated protein kinase 4 (MPK4) gene also has been reported to induce susceptibility. Loss of function mutant of *Glycine max* (soybean) MPK4 (GmMPK4) provided enhanced resistance to *Peronospora manshurica* (63). The silencing led to increased lignin biosynthesis, which helped to create a physical barrier and avoid penetration into the mesophyll.

Pathogen sustenance

The third class of S-genes includes genes that help in post-penetration sustenance of the pathogen by providing nourishment and synthesizing metabolites. Downy mildew resistant 1 (DMR1) gene encoding homoserine kinase (HSK), which catalyzes the biosynthesis of Met, Thr, and Ile; when mutated, provided resistance to *Hyaloperonospora parasitica* (64, 65), *H. arabidopsidis*, *Fusarium graminearum* and *F. culmorum* (66). These S-genes help by stopping the biosynthesis of amino acids (Met, Thr, and Ile), which produce substances toxic to the pathogen and hinder its presence. The genes encoding for SWEET proteins provide a carbon source and help in its sustainability (58, 67).

In rice, *Xanthomonas oryzae* use the SWEET S gene (OsSWEET14) through a transcription activator-like (TAL) effector protein AvrXa7 that binds at the promoter region of the S-gene and provides nutrition to bacterial cells (68). When the promoter region of this gene was edited using GE tools, its inability to bind with AvrXa7 led to reduced susceptibility and decreased expression of S-gene (69, 70).

The pathogen produces an effector that attacks specific targets in plants and induces susceptibility. Some plant translation factors are used by potyviruses for replication in plants. Mutant recessive S genes 4E and 4G (eIF4E/eIF4G) provided enhanced resistance against Potyviridae viruses (40). Mutated eIF4 gene in *A. thaliana* restricted viral movement within the plant and showed decreased susceptibility against cucumber mosaic virus (CMV) and turnip crinkle virus (TCV) (71).

The recent developments have led to new findings regarding S-genes and their role in disease development. Four new S-genes, including genes (WRKY transcription factor 6, Catalase protein, Shaggy-like protein kinase NtK-1 and OTU like cysteine protease), were identified in potato late blight disease (72).

S-gene mediated resistance in plants

Bacterial disease establishment depends on the interaction between type III effector genes and S-genes. The expression of S-gene *Os8N3* in rice during infection with *Xanthomonas oryzae* pv. *oryzae* strain PXO99A was studied. *Os8N3* is a member of the *MtN3* gene family and depends on the effector gene *pthXo1*. Silencing of *Os8N3* produced resistance to the PXO99A strain causing bacterial blight in rice (73).

Suppression or knockdown of S-genes can help in activating plant immune response and reduce susceptibility. The PAP2 gene encoding phosphatidic acid phosphatase was identified as an S-gee in *N. benthamiana* infected by *Ralstonia solanacearum*. Silencing of PAP2 reduced the susceptibility and increased the resistance to *R. solanacearum.* The silenced plants, when infected with the bacteria, led to over-accumulation of reactive oxygen species (ROS) and increased PR-4 expression, indicating a relation to the activation of plant defense (74).

In Arabidopsis, Defense No Death 1 (DND1) is an S-gene, and its mutant provides broad resistance against various fungi, bacteria, and viruses. Various S-genes initially identified in Arabidopsis have also been reported as functionally conserved in other plants. A study to validate its role in the late blight susceptibility of tomato and potato using RNAi was carried out. The suppression of DND1 in potatoes and tomatoes provided broad-spectrum resistance to late blight (*Phytophthora infestans*) and PM (*Oidium neolycopersici* and *Golovinomyces orontii*), showing the conserved nature of DND1 in tomato and potato. In a study, 11 S-genes from *A. thaliana* were selected, and orthologous genes were silenced in a highly susceptible late blight potato cultivar (Desiree). Silencing of five genes provided resistance to the *P. infestans* isolate Pic99189, while that of the sixth S-gene reduced susceptibility (75).

A set of the ortholog of the Arabidopsis S gene (DND1, DMR6, DMR1, and PMR4) was selected and studied in potatoes and tomatoes for their role in *B. cinerea* infection. DND1 helps in conidial germination and attachment

of pathogens. Silencing of DND1 in both plants showed reduced lesions compared to control plants as the aforementioned processes are hindered. Silencing of DMR6 in potato plants also showed reduced lesion size. Silencing of DMR1 and PMR4 in potato transformants did not show any change as compared to control plants. These results suggest the efficacy of S genes in resistance breeding (76).

The role of StVIK (*S. tuberosum* Vascular HIGHWAY1 [VH1]–INTERACTING KINASE [VIK]) encoding a MAP3K in *P. infestans* colonization in *N. benthamiana* was analyzed using VIGS. The silencing led to decreased colonization, indicating the potency of StVIK as a susceptibility factor. Thus, StVIK is exploited by *P. infestans* as a susceptibility factor to promote late blight disease (77).

The intricate relationship between the effector and S-gene/factor for pathogen establishment and colonization has been studied in *P. infestans* effector (Pi02860) and S factor (NRL1). NRL1 inhibits the expression of INF1-triggered cell death (ICD), helping in pathogen infection. NRL1 interacts with SWAP70, which helps in providing immunity in the plant. The silencing of SWAP70 in *N. benthamiana* through VIGS enhanced colonization and disease susceptibility. Thus, surpassing the defense responses with the help of NLR1 through the degradation of SWAP70 would aid pathogen colonization (78). This type of study of S-gene interaction would help in mining the other S and R genes involved in plant disease and open new avenues for plant disease management.

Pleiotropic effects

The efforts for S-gene-mediated resistance are limited due to the cost the plant has to pay for it. The alteration in the S gene is sometimes accompanied by a few side effects referred to as pleiotropic effects. These effects include dwarfing, decreased yield and fertility, early senescence, and increased susceptibility to other stress. Many S-genes and their pleiotropic effects have been studied (Table 1). Minimization of pleiotropic effects would ensure efficient use of S-genes. The use of native promoters would help in reducing the negative effects (75). Recently, a new gene-editing technology named CRISPR for improving agronomic traits in plants has been introduced. It has been used in various plant species, for instance, rice, wheat, and maize. Employing S-genes for introducing resistance in plants using CRISPR provides durable resistance and has been practiced in controlling many plant diseases.

Transgenic PM-tolerant wheat was produced by disrupting TaMLO-A1, TaMLO-B1, and TaMLO-D1 (79). PM-resistant wheat was developed by targeting TaEDR1 (three homologs) (80). Vegetative crops like tomato disruption of DMR6 provided resistance to *Pseudomonas syringae*, *Phytophthora capsici*, and *Xanthomonas* spp. (81). Almost complete canker disease resistance was observed in the case of Citrus after the degradation of promoter CsLOB1 (82). Transgene-free plants with improved quality/traits have also been developed using CRISPR and are commercially available in the USA, such as mushrooms, maize, soybean, and bristlegrass (83). Few other examples of transgene-free crops developed have been discussed. In the case of tomato, PM resistant crop was obtained by degrading S-gene SlMlo1 (84). In Arabidopsis, disruption of eIF4E provided resistance to TuMV (85). The degradation of eIF4E provided resistance to various viruses, including CVYV (ipomovirus), ZYMV, and PRSMV (potyvirus) (86).

Targeting promoters through CRISPR can help in reducing the chances of pleiotropic effects such as SWEET genes (40). Creating similar S-gene variants and introducing them in host rather than S-gene knockout presents another useful approach to surpass the pleiotropic effects. This approach has been used, and no pleiotropic effects were reported. Editing the S-gene allele at the single-nucleotide level (SNP) can also help in inducing resistance by introducing a variant of S-gene. These systems were shown to display no detectable off-target effects. A toolbox of a CRISPR vector system that can utilize pathogen-inducible promoters is still needed (87). Thus, the

Table 1. List of few S-gene and their pleiotropic effects

Sl. No	S-gene	Crop	Pleiotropic effect	Function of S gene	Reference
1	MPK4 (Mitogen- activated protein kinase)	*Arabidopsis thaliana*	Dwarfism and lesions	Negative regulator of SAR	88
2	MYB3R-4 (Myb-related protein 3R-4)	*Arabidopsis thaliana*	Mild developmental defects	Regulates DNA endoreduplication/ hypertrophy	89
3	FERONIA	*Arabidopsis thaliana*	Developmental defects	Control of host cell entry	60
4	ATG2 (autophagy-related 2)	*Arabidopsis thaliana*	Early senescence	Regulation of autophagy and SA-dependent defence	90
5	PAPP2C (phytochrome-activated protein phosphatase 2C)	*Arabidopsis thaliana*	Developmental defects	Negative regulation of SA-dependent defence and RPW8.2	44
6	MLO (Mildew resistance locus)	Barley	Enhances susceptibility towards necrotrophic fungi	Resistance against powdery mildew	63
7	RACB (Rho-related protein racB)	Barley	Developmental defects	Helps in accommodating in haustorium	56, 91
8	BI-1 (BAX inhibitor-1)	Barley	Enhanced Susceptibility to necrotrophs	Suppression of penetration resistance and cell death	51, 92

9	SLN (Slender)	Barley	Developmental defects	Cell death regulation	93
10	CMPG1	Potato	Susceptibility to other pathogens	Basal immunity	94
11	DMR1 (Downy Mildew Resistant 1)	Potato	Dwarfing and color loss	Negative regulator of defense genes	95
12	DND1 (Defense No Death 1)	Potato	Dwarfing, autonecrosis and chlorosis	Regulates the SA levels	95
13	CMR1 (Cucumber mosaic resistance 1)	Potato	Dwarfing and chlorosis	Resistance to Cucumber mosaic virus isolate P0	95
14	MAPK5	Rice	Reduced tolerance to abiotic stress	Regulate expression of PR (Pathogenesis related) genes	96

probable effect that will be caused due to the alteration in S-gene function should be studied and anticipated to ensure the full potential of S-gene resistance.

Conclusion

Exploiting S genes for imparting/enhancing disease resistance provides an alternative disease control method that is more durable and effective. Although this S-gene-mediated disease resistance should not be at the cost of the plant's loss, therefore, the various important aspects called pleiotropic effects, such as plant dwarfing, level of resistance achieved, and feasibility of targeting multiple genes, should be considered beforehand. Therefore, efforts are required to eliminate the pleiotropic effects associated with and avail the full potential of S-gene. The need for the future is to identify more S-genes and unveil their role in S-gene-mediated resistance. This will help in better understanding the defense signalling pathways and unravelling the reason behind the durability offered by S-gene resistance. These findings will enrich our knowledge and help in future resistance breeding.

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Authors contributions

KT and UG designed the manuscript. KT, NS, SK, and UG revised susceptibility genes, pleiotropic effects, types of resistance and BS and VB revised the role of susceptibility genes. All the authors have contributed significantly.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.

Ethical issues: None.

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