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Review

Susceptibility Is New Resistance: Wheat *Susceptibility* Genes and Exploitation in Resistance Breeding

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Abstract: Adapted pathogens and pests seriously threaten global wheat production. During pathogen and pest infections, wheat *susceptibility* (*S*) genes are exploited to support the compatibility of wheat with pathogens and pests. A plethora of wheat *S* genes were recently identified and revealed to regulate multiple processes, including pathogen (pre)penetration, plant immunity, pathogen sustenance, and pest feeding. The inactivation of some *S* genes via newly developed genome editing and TILLING techniques could reduce compatibility and confer broad-spectrum and durable resistance, which provide a new avenue for wheat resistance improvement. In this review, we summarized recent advances in the characterization of wheat *S* genes and highlighted their multifaceted roles in facilitating compatible interactions of wheat with adapted pathogens and pests. Current strategies, limitations, and future directions in exploiting *S* genes in wheat resistance breeding are discussed.

Keywords: wheat; susceptibility genes; resistance; pathogens; pests; genome editing; TILLING; (pre)penetration; plant immunity; pathogen sustenance

Citation: Li, M.; Yang, Z.; Chang, C. Susceptibility Is New Resistance: Wheat *Susceptibility* Genes and Exploitation in Resistance Breeding. *Agriculture* **2022**, *12*, 1419. https://doi.org/10.3390/agriculture12091419

Academic Editor: Roy Kennedy

Received: 14 August 2022
Accepted: 7 September 2022
Published: 8 September 2022

1. Introduction

As one of the most important staple crops, hexaploid bread wheat (*Triticum aestivum*) originated in the fertile crescent about 8500 years ago, and supplies approximately 20% of dietary calories and proteins for humans [1]. A growing population and overconsumption increased global demand for wheat grain. However, wheat yield and quality are reduced by attacks from adapted pathogens and pests (P&Ps) [2,3]. For instance, each of these eight devastating P&Ps (leaf rust, stripe rust, powdery mildew, *Fusarium* head blight, Septoria tritici blotch, spot blotch, tan spot, and aphid) caused wheat yield losses of more than 1% globally [2]. Therefore, breeding resistant varieties is essential for securing wheat production under P&P threats.

During the coevolution of plants with their parasites, plants acquired sophisticated immune mechanisms to cope with P&Ps infections, which provide valuable genetic resources for crop resistance breeding [4]. Typically, pattern-triggered immunity (PTI) and effector-triggered immunity (ETI) represent two intertwined layers of induced defense systems [5]. Pattern recognition receptors (PRRs) and nucleotide-binding domain leucine-rich repeat-containing receptors (NLRs) responsible for triggering PTI and ETI are widely deployed in crop resistance breeding [6–8]. However, this PRR/NLR-based dominant resistance is readily overcome by P&Ps that evolved to suppress or evade PTI/ETI [6–8]. To establish and maintain sustained compatibility between host plants and adapted P&Ps, plant *susceptibility* (*S*) genes are extensively exploited by P&Ps [9]. Notably, modifying some *S* genes via genome editing and targeting induced local lesions in genomes (TILLING) could confer wheat broad-spectrum and durable resistance, which might represent a new promising strategy in wheat resistance breeding [5,10,11]. Herein, we highlight recent developments in the understanding of wheat *S* genes and discuss strategies, challenges, and perspectives on exploiting wheat *S* genes for resistance improvement.

2. Wheat *S* Genes Supporting Pathogen (Pre)Penetration

Successful pathogen (pre)penetration is a prerequisite for the establishment of compatibility between plants and adapted pathogens. As an adaptive innovation in land plants, lipophilic cuticle covers the plant aerial surface and contributes to plant adaptation to environmental stresses such as drought, salinity, extreme temperatures, and ultraviolet radiation [12,13]. Increasing evidence reveals that wheat surface cues from cuticle induce pre-penetration development of adapted fungal pathogens [14,15]. For instance, the silencing of *TaWIN1*, a regulator gene in wheat cuticle biosynthesis, via virus-induced gene silencing (VIGS), results in the attenuated biosynthesis of cuticle and reduced conidial germination of fungal pathogen powdery mildew (*Blumeria graminis* f. sp. *tritici*, *Bgt*) [16]. Interestingly, exogenous application of wax very-long-chain (VLC, >C20) aldehydes absent from cuticle wax of the *TaWIN1*-silenced plants could fully rescue the *Bgt* germination penalty, suggesting that wax VLC aldehydes biosynthesis positively regulated by *TaWIN1* is exploited by *Bgt* for triggering conidial germination [16]. Consistent with this, VIGS of *TaKCS6* and *TaECR* in bread wheat results in attenuated wax biosynthesis and decreased *Bgt* germination [17,18]. *Bgt* germination penalty on *TaKCS6*- or *TaECR*-silenced plants is restored by the application of cuticular wax extracted from wild-type wheat plants [17,18]. These studies support the idea that wheat cuticle biosynthesis genes *TaWIN1*, *TaKCS6*, and *TaECR* are exploited by *Bgt* as *S* genes to support its pre-penetration development.

In addition to these *S* genes contributing to *Bgt* pre-penetration development, wheat genes essential for *Bgt* penetration have also been identified. As an *S* gene initially identified in barley, *mildew resistance locus O* (MLO) encodes a transmembrane protein, and is essential for powdery mildew penetration in a wide range of monocots and dicots [19–24]. Knockout of *TaMLO* using genome editing, TILLING, or VIGS results in the enhanced wheat penetration resistance to *Bgt* [25–28]. At the same time, microcolony formation of *Bgt* is attenuated in the *TaMLO* mutant, indicating that *TaMLO* could confer additional post-penetration resistance to *Bgt* infection [26]. Indeed, *HvMLO*, a barley ortholog of *TaMLO*, was revealed to suppress plant defense responses such as reactive oxygen species (ROS) burst and cell death at the infection site of barley powdery mildew (*Blumeria graminis* f. sp. *hordei*, *Bgh*) [19]. Notably, *MLO*-based barley resistance against *Bgh* relies on vesicular trafficking and actin reorganization, but not defense-related hormones, suggesting that vesicle/membranedynamics are involved in the *MLO*-mediated resistance against powdery mildew [24].

3. Wheat *S* Genes Suppressing Plant Immunity

Upon the perception of invading adapted P&Ps, plants initiate the induced defense systems, which typically leads to transcriptome reprogramming, calcium (Ca^{2+}) influx, reactive oxygen species (ROS) production, callose deposition, and even localized cell death (hypersensitive response, HR) [4,5]. In addition, the biosynthesis and signaling of defense-related phytohormones salicylic acid (SA), jasmonic acid (JA), and ethylene (ET) are usually activated to potentiate plant immunity [29]. In the absence of P&P infections, these defense-related responses need to be suppressed to favor plant normal growth and development [30].

As byproducts of aerobic metabolisms such as photosynthesis and respiration, ROS are continuously produced in plant chloroplasts, mitochondria, and peroxisomes [31,32]. In addition, plants evolved various peroxidases and oxidases to rapidly generate ROS in response to environmental stresses [31,32]. At the same time, a plethora of ROS-scavenging enzymes and non-enzymatic antioxidants are deployed to detoxify ROS in plant cells [31,32]. As an early defense signal in plant–pathogen interactions, ROS are generated locally and systemically to induce defense gene expression and trigger cell death [31,32]. Through promoting the regeneration of ROS-scavenging antioxidant ascorbic acid (AsA), monodehydroascorbate reductases (MDHARs) regulate the ROS level in plant cells [33]. The expression of the wheat *TaMDHAR4* gene is induced by ROS accumulation, and could respond to the infection of wheat stripe rust (*Puccinia striiformis* f. sp. *tritici*, *Pst*) [33]. The

silencing of *TaMDHAR4* by VIGS attenuates wheat susceptibility to *Pst* infection, suggesting that *TaMDHAR4* contributes to *Pst* infection by regulating ROS levels [33]. Similarly, the expression of a wheat alkaline/neutral invertases (A/N-Invs) gene *Ta-A/N-Inv1* is induced by *Pst* infection [34]. Notably, VIGS of *Ta-A/N-Inv1* results in the wheat H_2O_2 over-accumulation and enhanced cell death, as well as reduced susceptibility to *Pst* infection, indicating that wheat *S* gene *Ta-A/N-Inv1* is exploited by *Pst* to reduce H_2O_2 production and facilitate compatible interaction of wheat with *Pst* [34]. As summarized in Table 1 and Figure 1, wheat cytochrome b6-f component gene *TaISP* and Nudix hydrolase gene *TaNUDX23* are also harnessed by *Pst* to suppress ROS accumulation and contribute to compatibility between wheat and *Pst* [35,36].

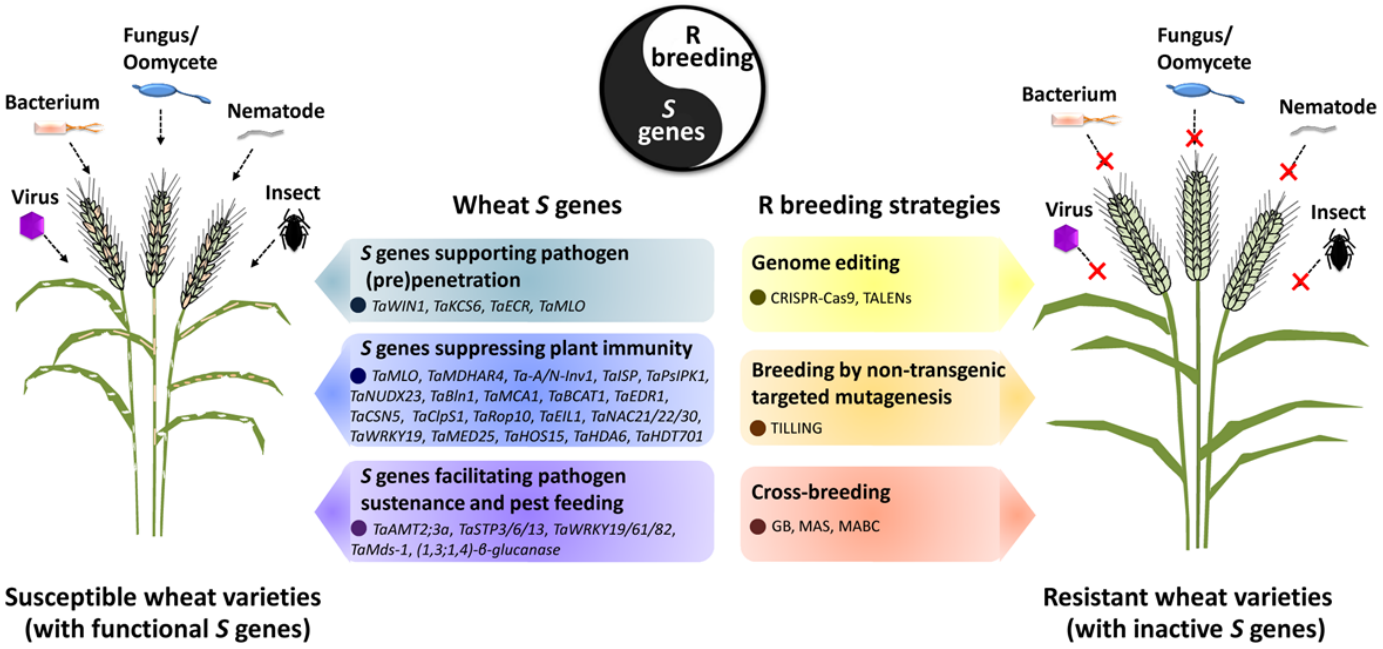

Figure 1. A schematic of targets and strategies for exploiting wheat *Susceptibility* (*S*) genes in resistance (R) breeding. Wheat *S* genes contribute to pathogen (pre)penetration, plant immunity, pathogen sustenance, and pest feeding. Inactivation of wheat *S* genes via genome editing, TILLING, and cross-breeding could reverse susceptibility and confer resistance to pathogen and pest infections.

Regulators of Ca^{2+} influx, cell death, and SA production were identified as wheat *S* genes contributing to the compatible interaction of wheat with *Pst* and *Bgt* [37–43]. The expression of wheat gene *Blufensin1* (*TaBln1*) is induced by *Pst* infection, and the wheat cysteine-rich peptide TaBln1 could interact with calmodulin TaCaM3 at the plasma membrane [37]. The silencing of wheat *TaBln1* results in the enhanced Ca^{2+} influx and attenuated accessibility to *Pst*, whereas VIGS of wheat *TaCaM3* decreases the Ca^{2+} influx and reduces wheat resistance to *Pst* [37]. These results implythat the wheat susceptibility factor TaBln1 impairs Ca^{2+} influx by interaction with TaCaM3, leading to the suppression of wheat defense and contributing to the compatibility between wheat and *Pst* [37]. Another wheat *S* gene *TaMCA1* encodes a metacaspase ortholog and could inhibit *Bax*-induced cell death when expressed in tobacco and wheat leaves [38]. Silencing of *TaMCA1* by VIGS enhances wheat resistance to *Pst*, implying that the wheat *S* gene *TaMCA1* facilitates compatibility between wheat and *Pst* by suppressing cell death [38]. In addition, the expression of wheat branched-chain amino acid (BCAA) aminotransferase gene *TaBCAT1* is potentiated during stripe rust development [39]. *TaBCAT1*-silenced wheat plants exhibit enhanced levels of BCAAs and SA, as well as attenuated susceptibility to *Pst*, suggesting that the *S* gene *TaBCAT1* promotes wheat accessibility to *Pst* via modulating BCAAs metabolisms and SA production [39].

Enhanced Disease Resistance 1 (*EDR1*) is initially identified from *Arabidopsis* and encodes a Raf-like mitogen-activated protein kinase kinasekinase (MAPKKK) [40]. The *Arabidopsisedr1* mutant exhibits mildew-induced mesophyll cell death and SA-dependent powdery mildew resistance [41,42]. Further studies reveal that *AtEDR1* negatively regulates *AtMPK3*, *AtMPK6*, and *AtATL1*, positive regulators in plant defense signaling and cell death, thereby suppressing plant immunity in *Arabidopsis* [43,44]. Notably, wheat *Taedr1* mutant generated by genome editing displays enhanced powdery mildew resistance without mildew-induced cell death and obvious growth penalty, suggesting that the wheat *S* gene mutant *Taedr1* might be a valuable resource in resistance breeding [45].

Components in protein degradation and Rho-of-Plant (ROPs) signaling pathways were identified as suppressors of wheat disease resistance [46–48]. The highly conserved constitutive photomorphogenesis 9 (COP9) signalosome (CSN) complex is involved in protein degradation via the ubiquitin–proteasome pathway [46]. Wheat COP9 subunit 5-like gene *TaCSN5* is induced during *Pst* infection, and *TaCSN5*-silenced wheat plants exhibit reduced susceptibility to *Pst* [46]. Another wheat *S* gene, *TaClpS1*, encodes a caseinolytic peptidase (Clp) protease, an adaptor mediating protein degradation, and is induced during stripe rust development [47]. Knockdown of *TaClpS1* expression via VIGS leads to the enhanced wheat resistance to *Pst*, whereas exogenous expression of *TaClpS1* in *Nicotiana benthamiana* promotes the infection of the oomycete pathogen *Phytophthora parasitica* [47]. These studies suggest that wheat protein degradation pathways involving *TaCSN5* and *TaClpS1* are exploited by *Pst* to suppress plant defense and promote compatible interactions of wheat with *Pst* [46,47]. As small GTP-binding proteins, plant ROPs are widely involved in the signaling processes in plant development and stress response [48]. The *TaRop10*-silenced wheat plant exhibits enhanced resistance to *Pst*, suggesting that the wheat ROP signaling pathway might be harnessed by *Pst* for promoting wheat accessibility to *Pst* [48].

As an integral part of plant immunity, the expression of defense genes is induced by P&P infections [49]. A plethora of wheat transcriptional and epigenetic regulators suppressing plant defense gene expression have been identified [49]. For instance, the silencing of wheat transcription factor genes *TaEIL1* and *TaNAC21/22/30* via VIGS potentiates defense gene expression and enhances disease resistance against stripe rust [50–52]. Wheat susceptibility factor TaMED25, a mediator subunit, interacts with TaEIL1 to activate *TaERF1* expression, and negatively regulates powdery mildew resistance, indicating the involvement of wheat mediator genes in the establishment of compatible interactions between wheat and *Bgt* [53]. The wheat receptor-like cytoplasmic kinase TaPsIPK1 was recently demonstrated to phosphorylate the transcription factor TaCBF1d for the transcriptional switch to defense suppression [54]. Interestingly, wheat transcription factor TaWRKY19 was shown to directly bind to promoter regions of *TaNOX10*, a NADPH oxidase gene involved in ROS production, and represses *TaNOX10* expression [55]. Expression of *TaWRKY19* is induced upon *Pst* infection, whereas *TaWRKY19*-silenced or *TaWRKY19*-knockout wheat plants exhibit both enhanced ROS accumulation and increased stripe rust resistance [55]. This evidence supports the idea that wheat susceptibility factor TaWRKY19 negatively regulates ROS production and *Pst* resistance via transcriptional suppression of *TaNOX10.*

As an important epigenetic mechanism, histone (de)acetylation plays an important role in the regulation of plant direct defense response and immune memory [56–58]. Generally, histone acetylation catalyzed by histone acetyltransferase contributes to gene activation, whereas histone deacetylation mediated by histone deacetylases is associated with gene suppression [56,57]. Wheat *S* genes *TaHDA6* and *TaHDT701* encode histone deacetylases and are induced during powdery mildew development [59,60]. TaHDA6 and TaHDT701 are shown to interact with WD40-repeat protein TaHOS15 and bind to promoter regions of defense genes such as *TaPR1*, *TaPR2*, *TaPR5*, and *TaWRKY45* [59,60]. The silencing of *TaHDA6*, *TaHOS15*, and *TaHDT701* potentiates histone acetylation in defense genes, leading to the enhanced expression of defense genes and potentiated powdery mildew resistance [59,60]. These studies suggest that wheat susceptibility factors TaHDA6, TaHOS15, and TaHDT701 repress plant resistance to *Bgt* via epigenetic suppression of defense genes.

Table 1. Summary of wheat *susceptibility* (*S*) genes contributing to pathogen and pest infections and their application in wheat resistance breeding. Class 1: pathogen (pre)penetration. Class 2: plant immunity. Class 3: pathogen sustenance. Class 4: pest feeding.

Class	Wheat *S* Gene	*S* Gene Product Family	Pathogen/ Pest Species	Contributions of Wheat *S* Genes to P&P Infections and Evidence	Application of *S* Genes in Resistance Breeding	Effector Targets	Reference
1	*TaWIN1*	AP2-EREBP-type transcription factor	*Blumeria graminis* f. sp. *tritici* (*Bgt*)	Silencing of *TaWIN1* by VIGS results in attenuated *Bgt* conidial germination.	None reported	None reported	[16]
1	*TaKCS6*	3-Ketoacyl-CoA synthase	*Bgt*	Silencing of *TaKCS6* by VIGS leads to reduced *Bgt* conidial germination.	None reported	None reported	[17]
1	*TaECR*	Enoyl-CoA reductase	*Bgt*	Silencing of *TaECR* by VIGS results in decreased *Bgt* conidial germination.	None reported	None reported	[18]
1, 2	*TaMLO*	Integral membrane protein	*Bgt*	Knockout *TaMLO* by TILLING enhances wheat penetration and post-penetration resistance to *Bgt*.	Wheat *Tamlo-R32* mutant generated by genome editing confers *Bgt* resistance without yield penalty.	None reported	[25–28]
2	*TaMDHAR4*	Monodehydroascorbate reductase	*Puccinia striiformis* f. sp. *Tritici* (*Pst*)	Silencing of *TaMDHAR4* by VIGS attenuates wheat susceptibility to *Pst* infection	None reported	None reported	[33]
2	*Ta-A/N-Inv1*	Alkaline/neutral invertase	*Pst*	VIGS of *Ta-A/N-Inv1* results in the wheat H_2O_2 over- accumulation, enhanced cell death, and reduced susceptibility to *Pst* infection	None reported	None reported	[34]
2	*TaISP*	Cytochrome b6-f component	*Pst*	Silencing of *TaISP* by VIGS reduces wheat photosynthesis and susceptibility to *Pst*.	None reported	Pst_12806	[35]
2	*TaNUDX23*	Nudix hydrolase	*Pst*	Knocking down of *TaNUDX23* expression by VIGS attenuates *Pst* infection.	None reported	Pst18363	[36]
2	*TaBln1*	Cysteine-rich peptide	*Pst*	Silencing of *TaBln1* results in the enhanced Ca^{2+} influx and attenuated accessibility to *Pst*.	None reported	None reported	[37]
2	*TaMCA1*	Metacaspase	*Pst*	Knockdown of *TaMCA1* expression by VIGS enhances wheat resistance to *Pst*.	None reported	None reported	[38]
2	*TaBCAT1*	Branched-chain amino acid (BCAA) aminotransferase	*Pst*	*TaBCAT1*-silenced wheat plants exhibit enhanced levels of BCAAs and SA, as well as attenuated susceptibility to *Pst*.	None reported	None reported	[39]
2	*TaEDR1*	Raf-like mitogen-activated protein kinase kinasekinase (MAPKKK)	*Bgt*	Knockout of *TaEDR1* by TALENs results in attenuated wheat susceptibility to *Bgt*.	Wheat *Taedr1* mutant generated by TALENs displays enhanced *Bgt* resistance without *Bgt*-induced cell death and obvious growth penalty.	None reported	[45]
2	*TaCSN5*	COP9 subunit 5-like protein	*Pst*	*TaCSN5*-silenced wheat plants exhibit reduced susceptibility to *Pst*.	None reported	None reported	[46]

Table 1. *Cont.*

Class	Wheat *S* Gene	*S* Gene Product Family	Pathogen/ Pest Species	Contributions of Wheat *S* Genes to P&P Infections and Evidence	Application of *S* Genes in Resistance Breeding	Effector Targets	Reference
2	*TaClpS1*	Caseinolytic peptidase (Clp) protease	*Pst*	Knockdown of *TaClpS1* expression via VIGS leads to the enhanced wheat resistance to *Pst*.	None reported	None reported	[47]
2	*TaROP10*	Small GTP-binding protein	*Pst*	The *TaRop10*-silenced wheat plant exhibits enhanced resistance to *Pst*.	None reported	None reported	[48]
2	*TaEIL1*	ETHYLENE INSENSITIVE 3 (EIN3) family transcription factor	*Pst*	Silencing of *TaEIL1* via VIGS enhances disease resistance against stripe rust.	None reported	None reported	[50]
2	*TaNAC21/22/30*	NAC transcription factor	*Pst*	Silencing of *TaNAC21*, *TaNAC22*, and *TaNAC30* attenuates wheat susceptibility to stripe rust.	None reported	None reported	[51,52]
2	*TaMED25*	Mediator subunit	*Bgt*	Silencing of *TaMED25* by VIGS enhances wheat resistance to *Bgt*.	None reported	None reported	[53]
2	*TaPsIPK1*	Receptor-like cytoplasmic kinase	*Pst*	Overexpression of *TaPsIPK1* enhances wheat susceptibility to *Pst* infection, but the silencing of *TaPsIPK1* attenuates wheat susceptibility.	Inactivation of TaPsIPK1 by genome editing confers wheat broad-spectrum resistance against *Pst* without yield penalty.	PsSpg1	[54]
2	*TaWRKY19*	WRKY transcription factor	*Pst*	*TaWRKY19*-silenced or *TaWRKY19*-knockout wheat plants exhibit enhanced stripe rust resistance.	None reported	None reported	[55]
2	*TaHOS15*	WD40-repeat protein	*Bgt*	Overexpression of *TaHOS15* enhances wheat susceptibility to *Bgt* infection, but the silencing of *TaHOS15* attenuates wheat susceptibility.	None reported	None reported	[59]
2	*TaHDA6*	RPD3-type histone deacetylase	*Bgt*	Overexpression of TaHDA6 attenuates wheat powdery mildew resistance, but the silencing of TaHDA6 enhances wheat resistance.	None reported	None reported	[59]
2	*TaHDT701*	HD2-type histone deacetylase	*Bgt*	Overexpression of *TaHDT701* enhances wheat susceptibility to *Bgt* infection, but the silencing of *TaHDT701* attenuates wheat susceptibility.	None reported	None reported	[60]
3	*TaAMT2;3a*	NH_4^+ transporter	*Pst*	Impeded *Pst* growth is observed in the *TaAMT2;3a*-silenced wheat leaves.	None reported	None reported	[61]
3	*TaSTP3/6/13*	Sugartransporter	*Pst*	Silencing of *TaSTP3*, *TaSTP6*, and *TaSTP13* by VIGS reduces wheat susceptibility to *Pst*.	None reported	None reported	[62–65]
3	*TaWRKY19/61/82*	WRKY transcription factor	*Pst*	*Pst* growth is impeded in the *TaWRKY19/61/82*-silenced wheat leaves.	None reported	None reported	[65]
4	*TaMds-1*	Small heatshock protein	Hessian fly	Silencing of *TaMds-1* attenuates Hessian fly infestation.	None reported	None reported	[66]
4	*(1,3;1,4)-β-glucanase*	Glucanase	Russian wheat aphid (RWA)	Aphid reproduction is reduced in the *(1,3;1,4)-β-glucanase*-silenced wheat plants.	None reported	None reported	[67]

4. Wheat *S* Genes Facilitating Pathogen Sustenance and Pest Feeding

Once the compatible interactions of wheat with adapted pathogens were established, pathogens acquired nutrients from wheat cells for growth and proliferation. There is increasing evidence that wheat nutrient transporter genes are widely exploited by pathogens for nutrient uptake and sustained compatibility [61–65]. Plant ammonium (NH_4^+) transporters are involved in the NH_4^+ uptake from soil and are responsible for maintaining nitrogen (N) status in plant cells [61]. It is reported that *Pst* infection leads to decreased NH_4^+ concentration and induces expression of the NH_4^+ transporter gene *TaAMT2;3a* in wheat leaves [61]. Interestingly, NH_4^+ concentration is enhanced by *Pst* infection in the *TaAMT2;3a*-silenced wheat leaves, which is accompanied by impeded *Pst* growth [61]. This evidence supports the idea that the NH_4^+ transporter gene *TaAMT2;3a* is exploited by *Pst* to facilitate NH_4^+ uptake from wheat cells and promotes pathogen infection and growth.

Sugar derived from wheat hosts serves as the major carbon (C) source taken upby phytopathogens. Increasing evidence reveals that adapted pathogens, especially biotrophic fungal pathogens, employ wheat sugar transporter genes for carbon uptake [62–65]. For instance, the wheat sugar transporter genes *TaSTP3*, *TaSTP6*, and *TaSTP13* are upregulated by *Pst* infection [63–65]. The wheat leaf rust (*Lr*) resistance gene *Lr67* was identified to encode an inactive mutant of *TaSTP13* [62]. Through heterodimerization with functional *TaSTP13*, LR67 exerts a dominant–negative effect to reduce wheat hexose accumulation for pathogen acquisition, and confers wheat partial resistance to all three rust pathogen species and powdery mildew [62]. Consistent with this, the silencing of *TaSTP3*, *TaSTP6*, and *TaSTP13* by VIGS reduces wheat susceptibility to *Pst*, whereas overexpression of these wheat sugar transporter genes in *Arabidopsis thaliana* leads to increased glucose accumulation and enhances susceptibility to powdery mildew (*Golovinomyces cichoracearum*) [63–65]. Notably, transcription factors TaWRKY19, TaWRKY61, and TaWRKY82 are demonstrated to activate the expression of *TaSTP3* induced by *Pst* infection, suggesting that the transcriptional activation of *TaSTP3* mediated by TaWRKY19/61/82 is exploited for the sugar acquisition of adapted fungal pathogens [65].

During an infestation, insect pests such as Hessian fly and Russian wheat aphid (RWA) harness wheat *S* genes for resource acquisition from host plants [66,67]. Wheat *S* gene *TaMds-1* (*Mayetiola destructor susceptibility-1*) encodes a small heatshock protein and is induced by the Hessian fly. Ectopic expression and heat induction of *TaMds-1* in resistant wheat variety confers susceptibility to Hessian fly [66]. In contrast, silencing of *TaMds-1* inhibits Hessian-fly-induced nutritive cell formation at the feeding site of host plants and attenuates Hessian fly infestation, suggesting wheat *S* gene *TaMds-1* isexploited for inducing wheat metabolic changes and nutritive cells formation, thereby contributing to nutrition acquisition and infestation of Hessian fly [66]. Another wheat *S* gene *(1,3;1,4)-β-glucanase* is highly upregulated during RWA infestation [67]. Aphid reproduction and plant symptom severity are reduced in the *(1,3;1,4)-β-glucanase*-silenced wheat plants, suggesting that wheat *S* gene *(1,3;1,4)-β-glucanase* contributes to aphid infestation [67].

5. Pathogen Effectors Targeting Wheat *S* Genes

To colonize and infect host plants, adapted P&Ps evolved effectors to manipulate plant immunity and metabolism [68,69]. Accumulating studies support the idea that pathogen effectors could target wheat *S* genes to facilitate infection [35,36,54]. Expression of *Pst* effector gene *Pst_12806* is induced during infection, and silencing of *Pst_12806* by host-induced gene silencing (HIGS) attenuates *Pst* infection [35]. Further studies reveal that Pst_12806 accumulates in wheat chloroplasts and interacts with TaISP, a subunit of the cytochrome b6-f complex [35]. Significantly, the silencing of *TaISP* by VIGS reduces wheat photosynthesis and susceptibility to *Pst*, whereas overexpression of *Pst_12806* in *N. benthamiana* attenuates photosynthesis, ROS production, and BAX-induced cell death [35]. This evidence suggests that effector protein *Pst_12806* inhibits the production of photosynthesis-derived ROS by interfering with the chloroplast protein TaISP, thereby attenuating plant immunity and contributing to *Pst* infection. Another effector gene *Pst18363* is also upregulated during

Pst infection, and the knockdown of *Pst18363* by HIGS compromises *Pst* infection [36]. *Pst18363* is found to bind and stabilize wheat Nudix hydrolase TaNUDX23, a negative regulator of ROS production, implicating that the effector protein Pst18363 suppresses ROS production to facilitate *Pst* infection by stabilizing TaNUDX23 [36]. Another *Pst* effector protein PsSpg1 was recently demonstrated to interact with the wheat susceptibility factor *TaPsIPK1*, a receptor-like cytoplasmic kinase, to potentiate its kinase activity and nuclear localization, thereby enhancing the wheat susceptibility to *Pst* [54]. Interestingly, knockout of *TaPsIPK1* could induce defense priming and confer broad-spectrum resistance to strip rust without yield penalty in the field, suggesting that the wheat *S* gene *TaPsIPK1* targeted by *Pst* effector PsSpg1 has great potential in resistance breeding [54].

6. Strategies and Challenges on Exploiting Wheat *S* Genes in Resistance Breeding

Wheat yield and grain quality are substantially reduced by P&P infections [2]. Breeding resistant varieties with durable and broad-spectrum resistance is one of the most effective strategies for controlling P&Ps and securing wheat production [70–72]. *Resistance* (*R*) genes mediating race-specific resistance and quantitative trait loci (QTLs) conferring partial resistance are widely employed in wheat resistance breeding. Single *R*/QTL-mediated resistance could readily be overcome by new pathogen races, which limits their application in crop breeding [6–8]. Stacking multiple *R* genes, combining *R* genes with QTLs, and engineering NLRs for expanded recognition specificity represent new promising strategies for crop resistance improvement [6–8]. As an alternative direction, the inactivation of *S* genes could effectively reverse susceptibility and confer crop resistance [70–72].

Advanced genome editing systems transcription activator-like effector nucleases (TALENs) and clustered regularly interspaced short palindromic repeats (CRISPR)–Cas (CRISPR–associated) are employed for engineering crop genomes and create new opportunities for the inactivation of wheat *S* genes [73–78]. Indeed, targeted knockout of *S* genes *TaWRKY19* and *TaPsIPK1* in wheat using CRISPR–Cas9 systems confers resistance to *Pst* [54,55]. Notably, the *Tapsipk1* mutant exhibits broad-spectrum resistance against *Pst* without yield penalty in field tests, suggesting that the *Tapsipk1* mutant is a valuable genetic resource for future wheat resistance breeding [54]. Genome editing of wheat *S* genes *TaMLO* and *TaEDR1* by TALENs enhances powdery mildew resistance [27,45]. Interestingly, wheat mutant *Tamlo-R32* generated by CRISPR–Cas9 systems confers robust powdery mildew resistance without yield penalty [28]. Further studies reveal that a 304-kilobase pair-targeted deletion in *Tamlo-R32* mutant causes changes in local chromatin structure and results in the activation of *Tonoplast monosaccharide transporter 3* (*TaTMT3B*), which could rescue the growth and yield penalties associated with *MLO* resistance [28]. This evidence supports the idea that genome editing of wheat *S* genes could effectively generate resistant varieties.

Conventional genome editing requires plant genetic transformation and regeneration, which hinders its use in recalcitrant crops like hexaploid bread wheat [75–78]. Wang et al. recently reported that the overexpression of the wheat gene *TaWOX5*, a regeneration-related gene of WUSCHEL family, could overcome genotype dependency and greatly enhance wheat transformation efficiency [79]. Debernardi et al. demonstrate that the expression of a chimeric protein harboring the wheat GROWTH-REGULATING FACTOR 4 (GRF4) and its cofactor GRF-INTERACTING FACTOR 1 (GIF1) improves the regeneration efficiency of transgenic wheat plants. These emerging techniques in wheat transformation and regeneration enhance the capacity for the inactivation of wheat *S* genes by conventional genome editing [80]. Through engineering a Barley stripe mosaic virus-based sgRNA delivery vector (BSMV-sg), Li et al. recently performed a heritable genome editing in Cas9 transgenic wheat plants via virus infection. Genome-edited progenies were obtained at frequencies of 12.9–100%, and most of the mutants are virus free [81]. This convenient and tissue culture-free approach for genome editing paves a new path for the manipulation of *S* genes and resistance breeding in bread wheat [81].

TILLING utilizes chemical mutagenesis and high-throughput screening approaches to generate the single-nucleotide mutations in targeted genome regions such as *S* genes of

interest [82]. Through introducing saturated mutagenesis, TILLING could be applied in hexaploid bread wheat [83]. Acevedo-Garcia et al. crossed *TaMLO* mutant lines identified in the TILLING screen and successfully created triple homozygous *TaMLO* lines that display enhanced *Bgt* resistance [26]. Since TILLING-derived crop varieties are accepted as non-transgenic, the targeted mutagenesis of wheat *S* genes by TILLING might provide a great opportunity for commercial resistance breeding [84]. In addition, *S* gene mutations generated by genome editing and TILLING could be introduced into elite wheat cultivars through cross-breeding, which is facilitated by advanced genomic breeding (GB) methods such as marker-assisted selection (MAS) and marker-assisted backcrossing (MABC) [85–87].

Although the past decades have seen substantial progress in identifying wheat *S* genes, we still have a long way to go towards fully uncovering the mechanism of wheat *S* genes facilitating P&P infections. For instance, most the characterized wheat *S* genes are revealed to facilitate infection of biotrophic fungal pathogens such as *Pst* and *Bgt*, while *S* genes promoting wheat accessibility to other P&Ps, especially insect pests [88] and necrotrophic pathogens, are poorly understood. Furthermore, the rice *S* gene *OsPIP1;3* and citrus *S* gene *CsLOB1* contribute to effector translocation and symptom development, respectively, but the wheat *S* gene controlling these processes remains to be identified [89–92]. Moreover, temperature changes could affect the stability and durability of disease resistance conferred by some *R*/QTLs [93,94]. It is vital to analyze the temperature sensitivity of inactive *S* gene-based resistance, and identify temperature-insensitive inactive *S* genes to secure the wheat's durable resistance under a changing climate. In addition, *S* genes regulate many processes in plant development and stress adaptation, and the understanding of plant genetic pathways/networks involving *S* genes would facilitate their proper application in wheat breeding.

7. Concluding Remarks and Perspectives

In this review, we summarized recent progress in characterizing wheat *S* genes and their functions in regulating pathogen (pre)penetration, plant immunity, pathogen sustenance, and pest feeding, and highlighted effector proteins manipulating wheat *S* genes (Table 1). Strategies and challenges in exploiting wheat *S* genes for resistance improvement were discussed. As depicted in Figure 1, multiple breeding strategies such as genome editing, TILLING, and cross-breeding could be deployed to modulate *S* gene for improving wheat resistance. Although the inactivation of *S* genes could attenuate wheat susceptibility to some P&P infections, many challenges need to be addressed regarding the exploitation of *S* genes in wheat resistance breeding. For instance, fitness cost is usually associated with resistance conferred by the inactive *S* gene. Identifying new *S* genes whose mutation confers enhanced resistance without negative effects on wheat growth and yield would contribute to the germplasm innovation for future resistance breeding. Furthermore, evaluation of the resistance spectrum of inactive *S* genes is crucial for the design of broad-spectrum resistance via stacking multiple inactive *S* genes and/or combining inactive *S* genes with *R*/QTLs. This broad-spectrum resistance could effectively protect wheat plants from multi-virulent pathogen populations common in the field. Moreover, different parasites usually employ distinct strategies for infection. It is, therefore, vital for wheat breeders to identify new *S* genes conferring wheat broad-spectrum susceptibility to a wide range of P&Ps. In addition, the release of crop varieties generated by genome editing is unacceptable in some countries/regions. Therefore, the regulatory framework on genome editing needs to be modified in these countries/regions before the release of wheat varieties with edited *S* genes. With the progress in the understanding of wheat *S* gene and advances in biotechnologies, modulating *S* genes would greatly promote wheat resistance improvement.

Author Contributions: C.C., M.L. and Z.Y. wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by the National Natural Science Foundation of China (31701412), the Natural Science Foundation of Shandong Province (ZR2017BC109), the Qingdao Science and Technology Bureau Fund (17-1-1-50-jch), and the Qingdao University Fund (DC1900005385).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We thank Xingguo Ye and Ke Wang for the kind invitation to write this review. We are also grateful to anonymous reviewers for their very helpful comments on this manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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