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Current Opinion in Plant Biology

Current understanding of atypical resistance against fungal pathogens in wheat

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Abstract

Pathogens and pests are a major challenge to global food security. Around one hundred different pests and pathogens challenge wheat, one of the most important food crops in the world. Traditional worldwide use of a few key resistance genes in wheat cultivars has necessitated a diversification of the toolbox of resistance genes in wheat varieties over the coming decades to meet the global production demands. Recent advances in gene discovery and functional characterization of genetic resistance mechanisms in wheat reveal great diversity in the types and effectiveness of the underlying resistance genes. This article summarizes the recent developments in the discovery of non-traditional "atypical" resistance genes in wheat against diverse fungal pathogens.

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Current Opinion in Plant Biology 2022, **68:**102247

This review comes from a themed issue on **Biotic interactions (2022)**

Edited by **Dr. Nidhi Rawat** and **Dr. Corné Pieterse**

For complete overview of the section, please refer the article collection - Biotic interactions (2022)

Available online 15 June 2022

https://doi.org/10.1016/j.pbi.2022.102247

Keywords

Wheat, Fungal pathogens, Atypical resistance, Broad-spectrum resistance (BSR).

Introduction

Wheat is one of the most important food crops covering more than 219 million ha and yielding more than 760 million tons annually [1]. It meets around 20% of the total daily caloric need of the global human population [2]. However, wheat production is impaired by various biotic and abiotic stresses [3,4]. Around 21.5% of wheat production is lost to fungal pathogens and insect pests globally every year [5]. Enhancing genetic resistance in wheat against fungal pathogens is critical to achieving global food security [6,7]. Recent advances in genome sequencing and annotation of different diploid, tetraploid, and hexaploid wheat genomes are facilitating unprecedented progress in the discovery and characterization of diverse resistance genes that will fortify wheat breeders' arsenal for resistance breeding against multiple pathogens [8–11].

In the quintessential interaction between a resistant plant and its biotrophic pathogen, the pathogen secretes proteins known as effectors in plant cells to facilitate infection, which are directly or indirectly detected by the host's resistance (R) proteins [12,13]. Since this interaction leads to the activation of a strong resistance response, known as effector-triggered immunity (ETI) in plants, the underlying pathogen effectors are called avirulence factors or Avrs [14]. Typical R proteins consist of nucleotide-binding leucine-rich repeat (NLR) proteins produced in the cytoplasm of the host cells. Rapid progress in the discovery and functional genomics of disease resistance genes in plants, including wheat, has revealed wide diversity in the type and their mechanisms of action, far exceeding the typical R-Avr interaction [15,16]. Examples of such atypical resistance genes include receptor-like kinases (RLKs), Wall-associated like receptor-like kinases (WAKs), Sugar and ATP binding cassette (ABC) transporters, tandem kinase proteins (TKPs), glutathione S-transferase (GST), Pore Forming Toxin-Like (PFT) and transcription factors (TFs). For this review, we have classified the non-canonical resistance genes as the atypical resistance genes. The atypical resistance proteins are not limited to the cytoplasm, and in fact, they can be categorized based on their cellular localization (Figure 1). This review article discusses recent discoveries made in the atypical resistance genes in wheat, grouped by the cellular location of the underlying predicted proteins (Table 1).

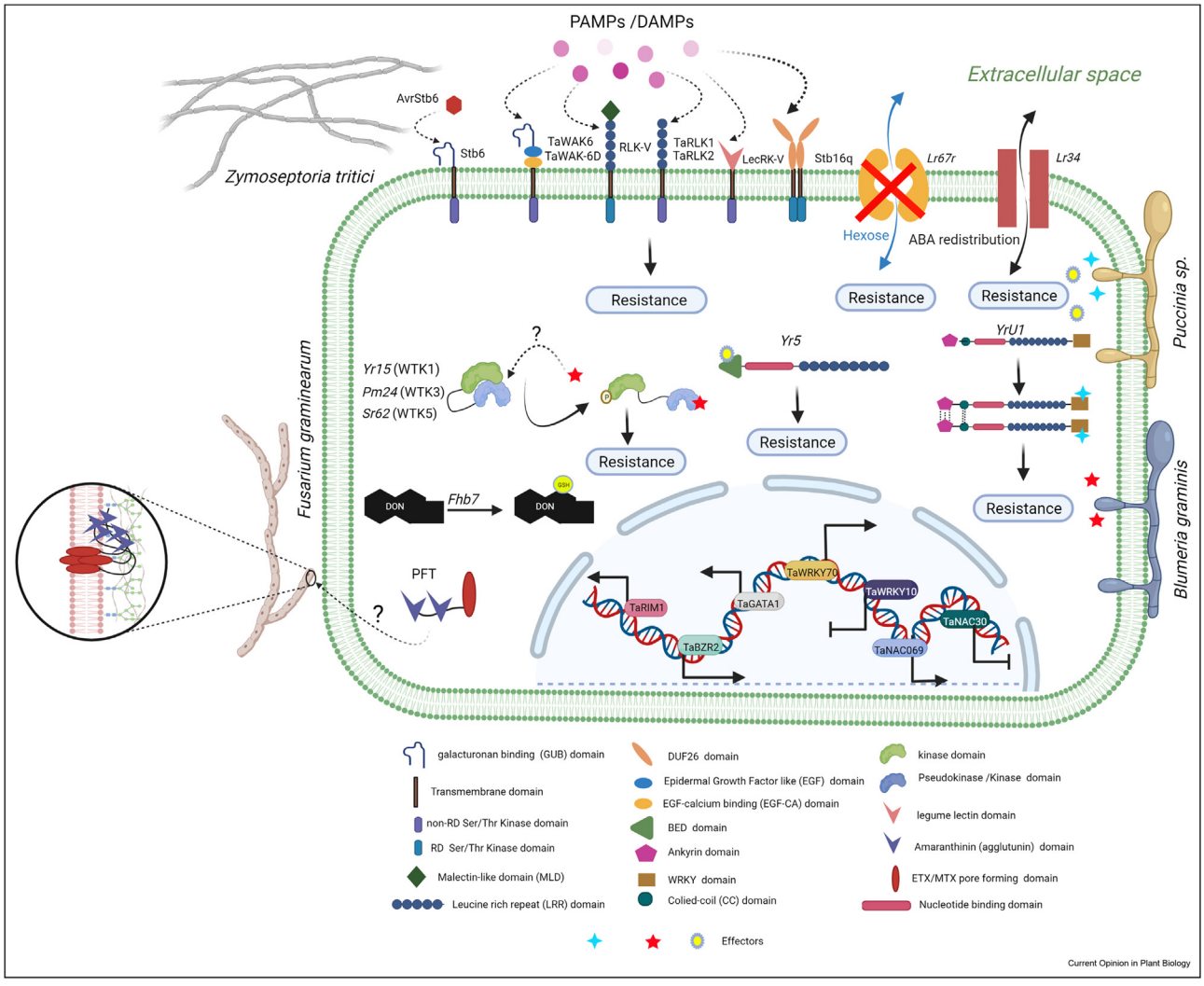
Cell wall and membrane

Perception and initial outcome of plant–pathogen interaction

The presence of microbes in the apoplastic space is detected by cell surface immune receptors that belong to membrane-associated RLKs or receptor-like proteins (RLPs). RLKs consist of an extracellular domain, a transmembrane domain, and a cytoplasmic kinase domain [17]. RLPs are similar in structure but lack the kinase domain. The diversity of extracellular ligand-binding domains of RLKs and RLPs has been used to classify them into different subclasses in model plants

Arabidopsis and rice [18]. Major classes include leucine-rich repeats (LRRs), lectin-like domain, cysteine-rich domain, lysine motif (LysM), epidermal growth factor (EGF)-like domain, and malectin-like domain (MLD) [19,20]. In wheat, *TaRLK1* and *TaRLK2* [21] and *RLK-V* and *LecRK-V* from *Haynaldia villosa*, a diploid wheat relative highly resistant to powdery mildew [22,23], have been shown to regulate wheat defense to powdery mildew pathogen *Blumeria graminis* f. sp. *tritici* (*Bgt*). *TaRLK1* and *TaRLK2* are LRR RLKs and their ectopic overexpression in wheat leads to increased production of reactive oxygen species (ROS) in fungal penetration sites leading to *Bgt* resistance [21]. *RLK-V* is a malectin-like/LRR-RLK that regulates both basal defense and *Pm21*-mediated resistance to *Bgt* [22]. *LecRK-V* is a lectin type RLK, whose overexpression confers *Bgt* resistance [23].

Figure 1



Schematic representation of Broad-spectrum resistance genes against fungal pathogens in wheat compartmentalized between extracellular spaces, cell membrane, cytoplasm, and nucleus. The extracellular and membrane-bound resistance genes have been categorized into receptor-like kinases (*TaRLK1*, *TaRLK2*), malectin-like/LRR-RLK (*RLK-V*), lectin type RLK (*LecRK-V*), cysteine-rich *RLK* (*Stb16q*), and wall-associated receptor-like kinases (*Stb6*, *TaWAK6*). The encoded proteins are involved in the perception of fungal determinants and transmitting the defense signal to the cell interior. Two other important membrane-bound atypical resistance genes encode for hexose transporters (Yr46/Lr67) and ABC transporters (Lr34) that confer BSR using a unique mechanism of inhibiting hexose transport and ABA redistribution, respectively. Intracellular BSR genes, covering a wide range of genes from NLR with atypical domains [BED (*Yr5*), Ankyrin and WRKY (*YrU1*)], wheat tandem kinase [WTK1 (*Yr15*), WTK3 (*pm24*), and WTK5 (*Sr62*)], GST (*Fhb7*), and PFT (*Fhb1*) utilizes diverse resistance mechanisms of defense against phytopathogenic fungus in wheat. Finally, nuclear transcription factors regulate the outcome of defense pathways by modulating the expression of defense-related and hormone-responsive genes. The different classes of TFs involved in wheat BSR are R2R3-MYB (TaRIM1), WRKY (TaWRKY70, TaWRKY10), NAC (TaNAC069, TaNAC30), BES/BZR (TaBZR2), and B-GATA (TaGATA1).

Table 1

List of non-canonical atypical resistance genes reported in wheat.

Localization	Gene	Gene product	Pathogen	Disease	Reference
Membrane	*Stb6*	Wall-associated receptor kinase (WAK)	*Zymoseptoria tritici*	Septoria tritici blotch	[28]
	TaWAK-6D	WAK	*Fusarium pseudograminearum*, and *Rhizoctonia cerealis*	Fusarium crown rot; sharp eyespot	[30]
	TaRLK1 and TaRLK2	leucine-rich-repeat (LRR) RLKs	*Blumeria graminis f. sp. tritici (Bgt)*	Powdery mildew	[21]
	RLK-V	Malectin-like/LRR-RLK	*Bgt*	Powdery mildew	[22]
	LecRK-V	Lectin type receptor-like kinase	*Bgt*	Powdery mildew	[23]
	TaWAK6	WAK	*Pt*	Leaf rust	[29]
	Stb16q	Cysteine-rich receptor like kinase (CRK)	*Z. tritici*	Septoria tritici blotch	[24]
	Yr46/Lr67	Hexose transporter	*Puccinia triticina* (*Pt*); *Puccinia striiformis f. sp. Tritici* (*Pst*); *Puccinia graminis* (*Pgt*); *Bgt*	Leaf rust; stripe rust; stem rust; powdery mildew	[31]
	Yr18/Lr34	ABC transporter	*Pt; Pst; Pgt; Bgt*	Leaf rust; stripe rust; stem rust; powdery mildew	[37]
Cytoplasm	*Yr5*	NLR and N terminal zinc-finger BED domain	*Pst*	Stripe rust	[48]
	YrU1	ANK-NLR-WRKY	*Pst*	stripe rust	[49]
	Yr15; YrG303; YrH52	Tandem kinase-pseudokinases	*Pst*	Stripe rust	[51]
	Pm24	Wheat tandem Kinase 3	*Bgt*	Powdery mildew	[54]
	Sr62	WTK5	*Pgt*	Stem rust	[55]
	Fhb7	Glutathione S-transferase	Fusarium spp.	Fusarium head blight	[56]
	Fhb1	Pore forming toxin-Like	Fusarium spp.	Fusarium head blight	[57]
Nucleus	*TaRIM1*	R2R3-MYB transcription factor	*R.cerealis*	Sharp eyespot	[58]
	TaWRKY70	Transcription factor	*Pst*	Stripe rust	[59]
	TaWRKY10	Transcription factor	*Z. tritici*	Septoria tritici blotch (STB)	[60]
	TaNAC069	NAC transcription factor	*Pt*	Leaf rust	[61]
	TaNAC30	NAC transcription factor	*Pst*	Stripe rust	[62]
	TaBZR2	Transcription factor	*Pst*	Stripe rust	[63]
	TaGATA1	B-GATA transcription factor	*R. cerealis*	Sharp eyespot	[64]

The extracellular domain in the members of the cysteine-rich RLK (CRK) subfamily consists of two DUF26 domains for ligand perception. Wheat gene *Stb16q* encoding a CRK confers a broad spectrum of resistance (BSR) against 11 isolates of *Zymoseptoria tritici*, causing Septoria tritici blotch [24]. One of the two DUF26 domain shares sequence similarity with the GNK2 mannose-binding domain, which suggests the affinity of extracellular *Stb16q* for apoplastic plant or fungi-derived mannose or its derivatives leading to *Stb16q*-mediated resistance [25]. Recognition of a conserved carbohydrate signature of the *Z. tritici* population by extracellular Stb16q stops the progression of pathogen either before its penetration through the stomata or into the sub-stomatal cavities [24].

WAKs represent a diverse cell surface immune receptor sub-family, specific to plants. WAKs confer resistance via different mechanisms ranging from non-specific quantitative resistance to a high level of specific resistance against particular races of pathogens [26]. Wheat *Stb6* gene, encodes a WAK-like protein, containing a secretory signal peptide, galacturonan-binding (GUB) domain, a transmembrane domain and a serine/threonine kinase domain. *Stb6* detects the presence of a matching apoplastic effector (*AvrStb6*) from *Z. tritici* and confers gene-for-gene resistance without a hypersensitive response [27,28]. Whereas, *TaWAK6*, a non-arginine-aspartate (non-RD) WAK, with an extracellular GUB domain, a calcium-binding epidermal growth factor (EGF_CA) domain, and a cytoplasmic serine/threonine kinase domain leads to quantitative partial resistance against *Puccinia triticina (Pt)* [29]. Another WAK, *TaWAK-6D* mediates a BSR against two different fungal pathogens: *Fusarium pseudograminearum* and *Rhizoctonia cerealis*, causing Fusarium crown rot and sharp eyespot diseases, respectively. TaWAK-6D protein includes a secretory signal peptide, an extracellular GUB domain closely connected to the cell wall, an EGF-like domain, an EGF domain, and an intracellular tyrosine kinase domain [30].

Transporters: the "gatekeepers" in wheat disease resistance

Membrane localized transporter proteins are vital to plant growth and development, and several studies have elucidated their role in biotic stress resistance. Sugar transporters are direct targets of pathogens to acquire carbohydrates for their growth and survival. A nonfunctional hexose transporter, resulting from mutations in two critical amino acids of *Yr46*/*Lr67*, confers BSR against multiple fungal pathogens including *Puccinia triticina* (leaf rust), *Puccinia striiformis* f. sp. *tritici* (*Pst*; stripe rust), *Puccinia graminis* f. sp. *tritici* (*Pgt*; stem rust), and (*Puccinia graminis* f. sp. *tritici*; *Pgt*) and, *Blumeria graminis* f. sp. *tritici* (*Bgt*; powdery mildew) in wheat [31,32]. Furthermore, *Lr67* conferred BSR in barley against *Puccinia hordei* and *B. graminis* f. sp. *hordei*, suggesting a conserved resistance mechanism between wheat and barley [33]. In addition to hexose transporters, sugars will eventually be exported transporters (SWEETs) are also exploited by pathogens to acquire carbohydrates in the extracellular space. Mutation of rice *OsSWEET11* has been shown to confer BSR against not only 63 diverse *Xanthomonas oryzae* races [34], but also against diverse *Rhizoctonia solani* (fungal pathogen causing sheath blight disease in rice) isolates in rice [35]. In wheat, a total of 108 *TaSWEETs* have been reported which show similarity with other 8 plant species that can be a good target for imparting resistance in wheat from *Pt* and *Pgt* conferring BSR [36].

ABC transporter encoded by *Lr34* (=*Yr18*/*Sr57*/*Pm38*) constitutes another important class that mediates quantitative BSR in wheat [37]. Transgenic expression of *Lr34res* in barley, rice, maize, and sorghum has been shown to enhance their resistance against various biotrophic or hemi-biotrophic fungal pathogens [38–41]. Recently, it was shown in wheat and barley that Abscisic Acid (ABA) is the substrate for the LR34 ABC transporter and *LR34res*-mediated ABA redistribution contributes to the resistance against multiple fungal pathogens [42,43].

Intracellular atypical resistance genes

Recently, various intracellular resistance genes with diverse atypical resistance mechanisms have been discovered in wheat. Intracellular plant receptors, which are typically NLRs, play a vital role in pathogen surveillance [44]. One of the recently emerged classes of non-canonical NLRs with atypical domain structures are NLRs with integrated domains (NLR-IDs) [45]. Like other plant species, wheat has a diverse set of IDs including kinases, DNA binding domains (AP2, B3, Myb-Like, WRKY, Zinc Finger), Jacalin-like lectin and ubiquitin-conjugating domains, etc. [46,47]In wheat currently, two NLR-IDs conferring BSR against multiple races of stripe rust pathogen *Pst* have been characterized. *Yr5* contains an N terminal zinc-finger BED domain that acts as a decoy, mimicking the target of pathogen effectors, leading to immunity against stripe rust in wheat [48]. *YrU1* encodes NLR-ID with two IDs: an N terminal ankyrin domain and a C-terminal WRKY domain. The homo-dimerization of coiled-coil and ankyrin repeats is critical for the activity of *YrU1* in resistance to stripe rust in wheat [49].

Lately, a novel class of intracellular receptors known as TKPs has emerged as class of atypical resistance proteins. TKPs consist of two kinase domains separated by a linker region [50]. In fact, five out of the six functionally characterized TKP in plants have been discovered in wheat and its relatives [51–55]. Notably, two of these TKPs, wheat tandem kinase 1 (WTK1) encoded

by *Yr15* and WTK3 encoded by *Pm24*, confer BSR against more than 3000 genetically diverse *Pst* isolates and 36 tested isolates of *Bgt*, respectively [51,54]. Recently, *Sr62*, another tandem kinase gene cloned from *Aegilops sharonensis*, a distant wild relative of wheat, was found to confer high levels of resistance against 12 geographically distinct *Pgt* isolates in wheat [55]. Based on mutation analysis, both the kinase domains of *Sr62* were required for resistance [55]. The molecular mechanism of TKP-mediated resistance is still not clear. It is proposed that the pseudokinase domain (or one of the kinase domains) could serve as a decoy for pathogen effector recognition and upon activation, kinase domain can initiate downstream defense signaling [50].

A mycotoxin detoxification gene is a new addition to intracellular atypical resistance genes in wheat. Cloning of *Fhb7* from *Thinopyrum elongatum*, a wild relative of wheat, revealed that it encodes a GST that irreversibly detoxifies trichothecene mycotoxins and provides resistance against Fusarium Head Blight (FHB) in wheat [56]. Moreover, *Fhb7* establishes a unique evolutionary path as it underwent horizontal gene transfer from an endophytic fungus *Epichloe* sp. to *T. elongatum* [56]. Another novel type of wheat atypical resistance protein is PFT protein. PFT is one of the major determinants of *Fhb1*-mediated BSR against FHB [57]. PFT is predicted to be a chimeric plant lectin with two amaranthin domains (agglutinin domains of *Amaranthus caudatus*) and one bacterial epsilon toxin (ETX)/mosquitocidal toxin (MTX) domain of aerolysin pore-forming toxin family. It is hypothesized that PFT interacts with the fungal cell walls via amaranthin domains and makes pores in the fungal membrane through ETX/MTX pore-forming domain, thereby killing the fungus [57]. This unique mechanism of defense against fungal pathogens can be widely applicable; however, it awaits further experimentation.

Nuclear regulation of disease response in wheat

In the nucleus, TFs modulate the expression of defense-related genes. Various families of TFs impart resistance against fungal pathogens in wheat. In a study on *R. cerealis*-wheat interaction, it was shown that a nuclear-localized TF *TaRIM1*, an R2R3-MYB, positively regulates defense response by modulating the expression of five defense genes (*Defensin, PR10, PR17c, nsLTP1*, and *chitinase1*) [58]. In another study, *TaWRKY70* was found to be associated with wheat high-temperature seedling plant resistance to *Pst*. Furthermore, *TaWRKY70* regulates the expression of Ethylene- and Salicylic Acid-responsive genes *TaPIE1* and *TaPR1.1*, respectively [59]. Recently another WRKY TF, *TaWRKY10* was found to negatively regulate the expression of JA receptor *TaCOI1*, thereby downregulating JA responses in *Z. tritici*-wheat interaction [60]. In a very recent study, the role of one of the NAC TFs, *TaNAC069* was found to positively regulate the wheat resistance to leaf rust fungus *Pt* by activating PR genes and inhibiting ROS clearance-related genes [61]. While another NAC, *TaNAC30* negatively regulates resistance in wheat-stripe rust pathogen (*Pst*) interaction as silencing of *TaNAC30* enhanced resistance by inducing a significant increase in the accumulation of H_2O_2 [62]. Another TF, *TaBZR2* targets the promoter region of the chitinase gene *TaCht20.2*, activating its transcription thereby conferring BSR to the stripe rust fungus by increasing total chitinase activity in wheat [63]. A wheat nuclear-localized LLM-domain containing B-GATA TF, TaGATA1, defends against *R. cerealis* infection by activating defense genes *PR10, PR17C*, and *Chitinase3* [64].

In addition to genetic regulation, epigenetic regulation with underlying DNA methylation is being investigated as an important aspect of defense regulation in wheat. Recent exploratory studies suggest that modulating DNA methylation enhances resistance against powdery mildew and FHB of wheat [65,66]. In addition, epigenetic regulation is also exploited by wheat fungal pathogens. For example, stem rust fungus *Pgt* uses an epigenetic silencing pathway similar to RNA-directed DNA methylation in plants [67]. *Pgt* induces an array of early and late infection small RNAs with differing profiles and up-regulates a subclass of RNAi genes regulating DNA methylation during late infection. Future host-induced gene silencing approaches may use this knowledge to utilize fungus's RNAi machinery to silence its important virulence genes [67].

Conclusion

Recent advances in wheat functional genomics have led to major breakthroughs in resistance gene discovery in wheat. Various new atypical resistance genes that may be effective against multiple races or even multiple species of pathogens have been characterized. Notably, these resistance genes have diverse mechanisms of action and encode proteins with non-canonical domain architecture. The diverse resistance mechanisms include pathogen surveillance, substrate transport, defense signaling, transcription regulation, pore formation, and toxin detoxification. Although several proposed mechanisms await experimental validation, the discovery of novel resistance genes is expanding our knowledge of plant immunity beyond traditional ETI. The promise of enhancing the extent of plant defense by these discoveries is exemplified by the transgenic incorporation of a cassette of five genes *Sr22—Sr35—Sr45—Sr50—Sr55* in wheat to achieve BSR against stem rust [68]. With the discovery of multiple atypical resistance genes with diverse underlying mechanisms, exciting opportunities exist to engineer specific domains and incorporate them in wheat cultivars to further enhance the level and range of genetic resistance against fungal pathogens.

Disclosure

Given her role as Guest Editor, Nidhi Rawat had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Corné Pieterse.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Acknowledgements

We would like to thank our funding agencies US National Science Foundation (Award number 1943155), USDA National Institute of Food, and Agriculture (Award number 2020-67013-32558), and US Wheat and Barley Scab Initiative (Award number 59-0206-0-179) for supporting our research.

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