REVIEW

Combatting Fusarium head blight: advances in molecular interactions between *Fusarium graminearum* and wheat

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Abstract

Fusarium head blight (FHB), mainly caused by *Fusarium graminearum*, is one of the most devastating diseases in wheat and barley worldwide. In addition to causing severe yield losses, *F. graminearum* produces deoxynivalenol (DON), a trichothecene mycotoxin which is harmful to human health and serves as an important virulence factor. Currently, changes in global climate and tillage systems have made FHB epidemics more frequent and severe. During the past decade, considerable efforts have been deployed to reveal the pathogenic mechanisms of *F. graminearum*, identify resistance genes in wheat, and breed FHB-resistant varieties. In this review, we highlight recent advances in FHB pathogenesis, *F. graminearum*-wheat interaction, and wheat defense mechanisms. This review contains four main sections: (1) signal sensing and transduction associated with the pathogenesis of *F. graminearum*; (2) regulation and functions of DON during wheat infection; (3) roles of *F. graminearum*-secreted enzymes and effectors in facilitating pathogen infection of wheat; (4) wheat components involved in interactions with *F. graminearum*. A comprehensive understanding of the molecular interactions between *F. graminearum* and wheat will contribute to the development of novel and efficient strategies for controlling FHB.

Keywords: FHB, Signaling pathway, Virulence factor, DON, Effector, Disease resistance, Susceptibility factor, Resistance improvement

Background

Wheat, one of the most important and highly nutritional cereals in the world, is used in the production of a diverse range of foods (Appels et al. 2018). It is a staple crop in Asia, Europe, North America, Australasia, as well as in other countries and regions (Hazard et al. 2020). Fusarium head blight (FHB), caused by *Fusarium graminearum*, is a notorious fungal disease affecting wheat and barley production worldwide (Walter et al. 2010; Jiang et al. 2020a). As global warming advances and the tillage system changes, the frequency and magnitude of FHB

epidemics have significantly increased in recent years (Chen et al. 2019; Zhu et al. 2019). In addition to causing severe yield losses and reducing grain quality, *F. graminearum* produces trichothecene mycotoxin deoxynivalenol (DON) and other toxic secondary metabolites (Ma et al. 2020). Due to the devastating nature of FHB, *F. graminearum* is ranked in the top 10 fungal pathogens in plant pathology (Dean et al. 2012).

FHB epidemics cause severe economic losses and pose a serious threat to human and animal health worldwide (Gorash et al. 2021). Since 1950, at least thirty FHB epidemics have been reported in China, occurring almost yearly during the past 20 years (Ma et al. 2020). FHB affects an average of over 4.5 million hectares, approximately 20% of which are planted with wheat, resulting in yield losses of over 3.41 million tons between 2000 and

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2018 (Chen et al. 2019). FHB was also considered the most destructive wheat disease in the USA (Wood et al. 1999) and caused a total loss of 17 billion U.S. dollars between 1993 and 2014 (Wood et al. 1999; Wilson et al. 2017). FHB epidemics were also reported in other wheat-growing countries, such as Canada, Brazil, Argentina, Paraguay, Uruguay, Hungary, and Poland (Dweba et al. 2017; Ma et al. 2020).

Although multidisciplinary efforts from phytopathologists, agronomists, breeders, commercial companies, and government research agencies have been conducted to control FHB, novel strategies for management of FHB still must be developed to face the continuous threat of the disease (Dweba et al. 2017). Here, we review the pathogenesis of *F. graminearum*, and the defense of wheat against infection by *F. graminearum*, providing new insights into the development of FHB control strategies and guiding wheat breeding programs to achieve resistance to FHB.

Signal sensing and transduction associated with the pathogenicity of *F. graminearum*

Infection and colonization of host plants by *F. graminearum*

As the main primary inoculum of FHB, *F. graminearum* ascospores are released from perithecia that are generated in infected residues of preceding crops or other non-crop plants (Dill-Macky and Jones 2000; Trail 2009). The ascospores adhere to the host surface and germinate to produce germ tubes. Hydrophobin proteins FgHyd2, FgHyd3, and FgHyd4 contribute to the attachment of ascospores to hydrophobic surfaces such as wheat spike tissues (Quarantin et al. 2019a). Attached germ tubes then develop into specialized unbranched hyphae known

as runner hyphae (RH). The RH grows epiphytically on the surface of the wheat spike and differentiates to generate multicellular infection cushions (IC) (Boenisch and Schäfer 2011). The IC penetrate plant cuticles and form multiple penetration sites to facilitate the initiation of infection (Mentges et al. 2020). In addition, small infection structures, such as lobate appressoria and foot structures, found on the wheat palea, may also be involved in the early stage of infection (Mentges et al. 2020). To investigate the molecular basis of infection structure formation, laser capture microdissection was used to isolate RH and IC (Mentges et al. 2020). RNA-seq and transcriptome analysis showed that a variety of infection-related genes such as carbohydrate-active enzymes (CAZymes), candidate effectors, and secondary metabolism gene clusters are upregulated in the IC relative to those in the RH (Mentges et al. 2020). During *F. graminearum* infection, IC act as both infection structures and arsenal. Upon infection, infection hyphae spread throughout the spikelet and the rachial node, and eventually grow through the rachis to reach the spikelets above and below the node (Dweba et al. 2017).

G-protein-coupled receptor and G-protein signaling pathways

Fungal signaling pathways are important for initial colonization and subsequent switches among different stages of plant infection (Fig. 1). Fungi utilize G-protein-coupled receptors (GPCRs) to sense environmental cues and in turn activate downstream signaling for the regulation of various biological processes (Brown et al. 2018). During infection of plants, fungal pathogens direct hyphal growth toward host-derived signals such as nutrients, wax, and hydrophobic surfaces (Turrà et al. 2015; Brown

(See figure on next page.)

Fig. 1 Pathogenesis-related signal sensing and transduction in *Fusarium graminearum*. During infection, GPCRs (Giv1-Giv3, FGRRES_16221, and FgSte2) and other cell membrane receptors (FgSho1, FgSln1, and FgMsb2) in *F. graminearum* sense various environmental and plant cues to activate intracellular G-protein, MAPK, cAMP-PKA signal pathways, and downstream transcription factors for regulating the differentiation of infection structures and hyphae, the secretion of pathogenicity factors such as cell wall- degrading enzyme and effector, and DON production. Three MAPK and cAMP-PKA signal pathways are required for DON production and full virulence of *F. graminearum*. FgSte50 is an adaptor protein in both Gpmk1 invasive growth (IG) and Mgv1 cell wall integrity (CWI) MAPK pathways. The FgSte11-FgSte7-Gpmk1 kinase cascade is responsible for signal transduction in the *F. graminearum* IG pathway. Transcription factors FgSte12, FgMcm1, and FgSfl1 are the downstream targets of Gpmk1. FgBck1-FgMkk1-FgMgv1 kinase cascade is responsible for signal transduction in the *F. graminearum* CWI MAPK pathway. The transcription factors Fgp1, FgRlm1, and FgSwi6 are potential downstream targets of FgMgv1. *F. graminearum* Hog1 is the MAPK that functions in the high-osmolarity glycerol (HOG) MAPK pathway, in which the response regulator protein FgRrg-1 is involved in wheat infection, and FgSsk2 and FgPbs2 act as the MEKK and MEK, respectively. ATF/CREB transcription factor FgAtf1 is the downstream target of FgHog1. The downstream transcription factors of MAPK pathway are involved in pathogenicity by regulating the expression of pathogenicity genes, including *TRI* genes, cell wall-degrading enzyme genes, and effector genes. The cAMP-PKA signaling pathway also plays an important role in the pathogenicity of *F. graminearum*. CPK1 and CPK2 (two catalytic subunits of PKA), PKR (the regulatory subunit of PKA), Fac1 (the adenylate cyclase), and FgCap1 (protein associated with the adenylate cyclase) are key components in the cAMP-PKA signaling pathway. FgSfl1 is one of the downstream transcription factors of PKA. FgAreA, a global regulator of nitrogen metabolism, interacts with Tri10 for the transcriptional regulation of *TRI* genes. *F. graminearum*-induced putrescine stimulates FgAreA to enter the nucleus. FgAreA binds to the promoter regions of *TRI* genes to rearrange the nucleosome array. The exposure of nucleosome-free regions subsequently facilitates the deposition of histone H2B monoubiquitination (H2B ub1) and histone 3 lysine 4 di- and trimethylations (H3K4 me2/3) on *TRI* genes, which further activates the expression of *TRI* genes and promotes DON biosynthesis and *F. graminearum* infection

Fig. 1 (See legend on previous page.)
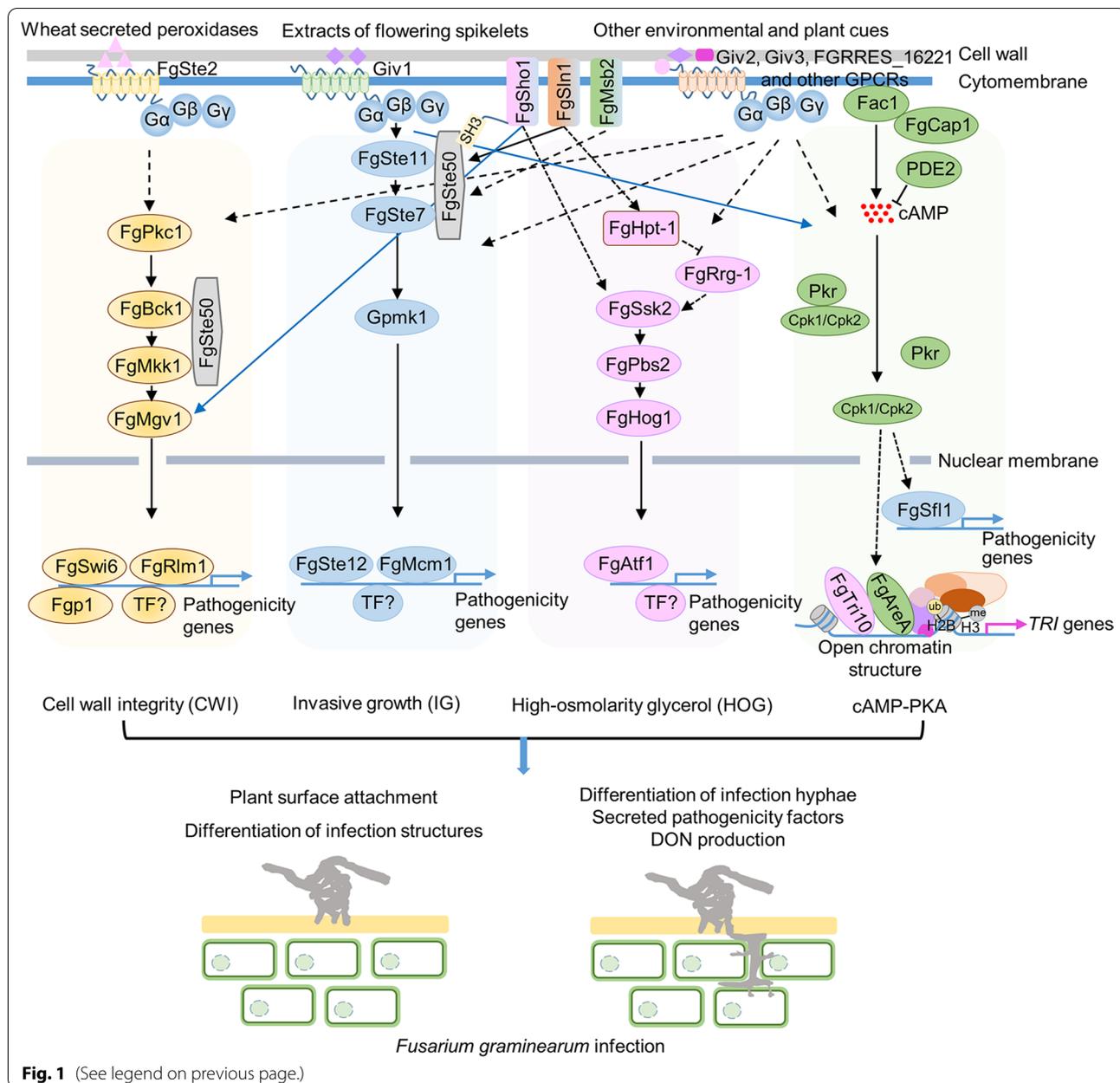
et al. 2018; Sridhar et al. 2020). A systematic characterization of 105 GPCR genes in *F. graminearum* demonstrated that five of them (*GIV1–GIV5*) are up-regulated during infection of plant and play crucial roles in the virulence of the pathogen (Jiang et al. 2018). Giv1 likely senses factors in wheat floral tissue for the regulation of IC formation through Gα Gpa2 and the cAMP-PKA pathways (Yu et al. 2008; Hu et al. 2014; Jiang et al. 2018). Giv1 also functions upstream of the Gpmk1 MAPK (PMK1) pathway which is also required for plant infection (Jenczmionka et al. 2003; Jiang et al. 2018, 2019). Although Giv2

and Giv3 have no effect on the initial infection of lemma tissues, they are involved in penetrating the rachis and spreading in the wheat spike (Jiang et al. 2018). Interestingly, *F. graminearum* has an expanded infection-related GPCR (EIG) gene subfamily including *GIV2–GIV6*. Comparative genomic analysis between *Magnaporthe oryzae* and *Neurospora crassa* suggests that GPCR genes in the EIG subfamily have expanded in phytopathogenic fungi, especially in *F. graminearum*. A total of 19 of the 22 EIG genes are in the fast-evolving genomic regions (Wang et al. 2017; Jiang et al. 2019), further indicating that this

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subfamily may be subjected to positive selection during the co-evolution of *F. graminearum* and wheat (Jiang et al. 2019). Another research group also showed that the expanded class X GPCRs (FGRRES_07792, accession number in the comprehensive reference annotation YL1 for PH-1: FG4G20870 and FGRRES_16221, accession number in the comprehensive reference annotation YL1 for PH-1: FG2G28420) interact with Gα subunits and are important for the virulence of *F. graminearum* (Dilks et al. 2019). FGRRES_16221 contributes to virulence by orchestrating the expression of some components in the fungal signaling pathway, such as GPCRs, G-proteins, cAMP-PKA, and MAPK, secondary metabolite genes, and putative secreted effector genes (Dilks et al. 2019). In addition, the pheromone receptor Ste2 in *F. graminearum* mediated the peroxidase-directed chemotropism that is associated with stimulation of the mitogen-activated protein kinase signaling cascade important for fungal cell wall integrity (Sridhar et al. 2020).

GPCRs are associated with intracellular heterotrimeric G proteins (Gα, Gβ, and Gγ) to regulate signal transduction. Once ligands are recognized by putative GPCRs, the heterotrimeric G-proteins will be dissociated into a GTP-binding Gα monomer and a Gβ/Gγ dimer, which in turn activates or inactivates the downstream signals by regulating downstream targets, such as phospholipases or adenylate cyclases (Brown et al. 2018; El-Defrawy and Hesham 2020). The genome of *F. graminearum* contains five heterotrimeric G protein genes, including three Gα subunits (GzGpa1, GzGpa2, and GzGpa3), one Gβ subunit GzGpb1, and one Gγ subunit GzGpg1. Deletion of *GzGPA2* or *GzGPB1*, but not *GzGPA1* or *GzGPA3* reduces the pathogenicity of *F. graminearum* (Yu et al. 2008). Repressors of G-protein signaling (RGS) proteins function primarily as GTPase-accelerating proteins to promote the hydrolysis rate of GTP bound to Gα, and then inactivate Gα and promote the formation of heterotrimeric G proteins, thus acting as negative regulators of G protein signaling (Xue et al. 2008). Three RGS proteins, FgFlbA, FgRgsA, and FgRgsB, were shown to be associated with the virulence of *F. graminearum* (Park et al. 2012).

MAPK and cAMP–PKA pathways
MAPK pathways play important roles in the responses to abiotic and biotic stresses in eukaryotic organisms. Typically, the MAPK pathway includes a kinase cascade, which comprises a MEK kinase (MEKK), a MAPK kinase (MEK), and a MAPK. The sequential activation of these kinases phosphorylates downstream transcription factors and other target proteins for the regulation of gene transcription associated with various biological processes (Zhang et al. 2021). Like most ascomycetous plant

pathogenic fungi, *F. graminearum* has three MAPKs (Gpmk1/Map1, Mgv1, and FgHog1) that are orthologous to *Saccharomyces cerevisiae* Fus3/Kss1, Slt2, and Hog1, respectively (Wang et al. 2011).

F. graminearum Gpmk1 (Map1) is orthologous to Fus3/Kss1, which is a component of the invasive growth (IG) MAPK pathway. Deletion of *GPMK1* (*MAP1*) results in loss of pathogenicity and a reduction in DON production at the initial inoculation site (Urban et al. 2003). In addition, Gpmk1 mediates the regulation of the early production of extracellular enzymes such as endoglucanases, xylanases, proteases, and lipases (Jenczmionka and Schäfer 2005). The FgSte11-FgSte7-Gpmk1 kinase cascade is responsible for signal transduction in the *F. graminearum* Gpmk1 (Map1) pathway. Deletion of the upstream *FgSTE11* (MEKK-coding gene) or *FgSTE7* (MEK-coding gene), results in similar phenotypic defects to those observed in *gpmk1* mutant during infection of wheat (Wang et al. 2011). A scaffold protein FgSte50 interacts with both FgSte11 and FgSte7, and the *Fgste50* deletion mutant is non-pathogenic towards the wheat head as well (Gu et al. 2015a). FgSte50, FgSte11, and FgSte7 are essential for the phosphorylation of Gpmk1 and activation of the IG MAPK pathway in *F. graminearum* (Ramamoorthy et al. 2007; Gu et al. 2015a). Transcription factors FgSte12 and FgMcm1 were identified as the downstream targets of Gpmk1 (Gu et al. 2015b; Yang et al. 2015; Zhang et al. 2021). Whereas FgSte12 is required for the secretion of cellulase and protease that are important for infection (Gu et al. 2015b), FgMcm1 is involved in the initial colonization and subsequent spread of *F. graminearum* throughout the wheat heads by regulating the expression of pathogenicity factors (Yang et al. 2015).

F. graminearum Mgv1, an ortholog of *S. cerevisiae* Slt2, is the MAPK of the cell wall integrity (CWI) MAPK pathway. Deletion of *MGV1* or its upstream *FgMKK1* or *FgBCK1* in this pathway results in hypersensitivity to cell wall stresses and severe defects in pathogenicity (Wang et al. 2011; Zheng et al. 2012). The transcription factors FgRlm1, FgSwi6, and Fgp1, are potential downstream targets of CWI MAPK signaling (Jonkers et al. 2012; Liu et al. 2013; Yun et al. 2014; Zhang et al. 2021). The *Fgrlm1* deletion mutant is hypersensitive to cell wall-damaging agents and defective in pathogenicity (Yun et al. 2014). In contrast, FgSwi6 is required for cellulose utilization, DON production, and virulence of *F. graminearum* (Liu et al. 2013). The Wor1-like protein Fgp1 is required for DON production and pathogenicity (Jonkers et al. 2012). Although the relationship between Mgv1 and Fgp1 remains to be investigated, MoGti1 (the ortholog of Fgp1) in *M. oryzae* is indirectly regulated by Mps1 (the ortholog of Mgv1) (Li et al. 2016).

F. graminearum Hog1 is the MAPK that functions in the high-osmolarity glycerol (HOG) MAPK pathway. The HOG pathway is associated with the two-component system consisting of an osmosensor histidine kinase FgSln1, a histidine phosphotransfer protein FgHpt-1, and two response regulator proteins FgRrg-1 and FgRrg-2 (Jiang et al. 2011; Zhang et al. 2021). Deletion of *FgRRG-1* largely abolished the virulence of *F. graminearum* on wheat heads (Jiang et al. 2011). FgSsk2 and FgPbs2 act as the MEKK and MEK in the HOG MAPK cascade, respectively. Deletion of three main components in this kinase cascade increases the sensitivity of *F. graminearum* to osmotic and oxidative stresses, which are likely related to defects in virulence (Wang et al. 2011; Zheng et al. 2012). ATF/CREB transcription factor FgAtf1 is a well-studied downstream target of FgHog1. Osmotic stress promotes the interaction between FgAtf1 and FgHog1 (FgOS-2) in the nucleus, and the *Fgatf1* deletion mutant is defective in wheat infection (van Nguyen et al. 2013).

Unlike its yeast ortholog, the osmosensor FgSho1 only plays a minor role in the response to osmotic stress in *F. graminearum* (Posas et al. 1996; Gu et al. 2015a, b). Instead, FgSho1 has an additive effect with FgSln1 on the pathogenicity of *F. graminearum* by physically interacting with the IG MAPK module FgSte50-Ste11-Ste7. In addition, the *Fgsho1* deletion mutant exhibited increased sensitivity to cell wall stress agents, which is consistent with that FgSho1 positively regulates phosphorylation of FgMgv1. Moreover, membrane mucin FgMsb2 may also function upstream of MAPK module FgSte50-Ste11-Ste7 (Gu et al. 2015a, b).

To determine the effects of MAPK-deficient strains of *F. graminearum*, mutants deleted of all three MAPK genes (*GPMK1/MAP1*, *MGV1*, and *FgHOG1*) were generated in a recent study (Ren et al. 2022). The *Gpmk1 mgv1 Fghog1* triple mutant is still viable but has severe defects in vegetative growth, conidiation, sexual reproduction, responses to various abiotic stresses, and bacterial- or fungal-fungal interactions. Moreover, the *Gpmk1 mgv1 Fghog1* triple mutant is non-pathogenic towards the wheat head, wheat coleoptile, and corn silks (Ren et al. 2022).

The cyclic AMP (cAMP)-dependent protein kinase A (PKA) signaling pathway is also an important signal transduction pathway in plant pathogenic fungi (Hu et al. 2014). In *F. graminearum*, *CPK1* and *CPK2* encode the catalytic subunit of PKA. Whereas the *cpk1* mutant was defective in the development of penetration branches on plant surfaces, colonization of wheat rachises, and spreading in flowering wheat heads, the *cpk2* mutant was normal in plant infection. Nevertheless, the *cpk1 cpk2* double mutant is nonpathogenic, suggesting that Cpk1 and Cpk2 have an overlapping function in pathogenesis

(Hu et al. 2014). PKR, the regulatory subunit of PKA plays a critical role in vegetative growth, viability of conidia, sexual reproduction, and plant infection (Li et al. 2018). In addition, the adenylate cyclase Fac1 and its associated protein FgCap1 were shown to be important for modulating the intracellular cAMP level and regulating vegetative and invasive growth of *F. graminearum* (Hu et al. 2014; Yin et al. 2018). In a recent study, FgSfl1 was characterized as a downstream transcription factor of PKA (Gong et al. 2021). Three PKA phosphorylation sites S223, T452, and S559 of FgSfl1 have distinct functions in fungal development and plant infection (Gong et al. 2021).

The regulation and functions of deoxynivalenol (DON) during infection of wheat

DON is an important virulence factor of *F. graminearum*

DON is a mycotoxin that binds to the ribosome to inhibit protein biosynthesis, resulting in disorders of cell signaling, differentiation, reproduction, and even teratogenicity in mammals (Pestka 2010; Chen et al. 2019). DON is also an important virulence factor of *F. graminearum* during infection of plants (Proctor et al. 1995; Bai et al. 2002; Jansen et al. 2005). The gene *TRI5* encodes trichodiene synthase, which catalyzes the first step in trichothecene biosynthesis, cyclizing farnesyl pyrophosphate (FPP) to trichodiene (Hohn and Beremand 1989). The *tri5* deletion mutant blocks DON production (Bai et al. 2002), and is restricted to the initially infected spikelets (Jansen et al. 2005), indicating that DON may facilitate the spread of *F. graminearum* throughout the wheat head. A comparative transcriptome study of symptomatic and symptomless wheat tissues revealed that *TRI* genes are highly induced in symptomless tissues, indicating a crucial role of DON in modulating host defenses and the establishment of infection (Brown et al. 2017). Metabolite profiling of *F. graminearum* wild-type and the *tri5* deletion mutant in infected rachis nodes provides evidence to support the role of DON in the suppression of host defense-related metabolites (Bonnighausen et al. 2019). DON was shown to modulate programmed cell death (PCD) of plant cells in a concentration-dependent manner (Diamond et al. 2008; Diamond et al. 2013). During infection, *F. graminearum* may produce a higher concentration of DON to elicit hydrogen peroxide production via increasing the size of hyphal colony, which further stimulates PCD in wheat (Diamond et al. 2008, 2013) and thus promotes its switch from biotrophy to necrotrophy (Bonnighausen et al. 2019).

The biosynthesis of DON

A total of 15 *TRI* genes, including *TRI5*, are responsible for DON biosynthesis. These *TRI* genes are located

at three different loci in the *F. graminearum* genome: a core *TRI* cluster that includes 12 genes, a *TRI1–TRI16* locus, and the *TRI101* locus (Alexander et al. 2009; Seong et al. 2009; Chen et al. 2019). Tri6 and Tri10 are considered as transcription factors regulating the expression of *TRI* genes. Chromatin immunoprecipitation sequencing (ChIP-Seq) revealed that Tri6 regulates genes involved in the biosynthesis and transport of DON, including *TRI1, TRI3, TRI6, TRI7, TRI12,* and *TRI14* (Nasmith et al. 2011). The *tri6* or *tri10* deletion mutants are significantly reduced in pathogenicity and DON production. Transcriptome analysis showed that Tri6 regulates not only the expression of *TRI* genes but also the upstream isoprenoid pathway of DON biosynthesis (Seong et al. 2009). Differentially expressed genes identified in the *tri10* deletion mutant are decreased in expression level relative to the *tri6* deletion mutant. A total of 73% of genes (including some *TRI* genes and isoprenoid biosynthesis-related genes) with altered expression levels in the *tri10* deletion mutant overlapped with those in the *tri6* deletion mutant. Tri6 is likely a global regulator while Tri10 tends to be a specific transcription factor of the *TRI* gene cluster (Seong et al. 2009). Two cytochrome P450 oxygenases (Tri1 and Tri4) are localized to the remodeled endoplasmic reticulum, named toxisome, which is involved in early and late steps in DON biosynthesis under *TRI*-inducing conditions and during plant infection (Menke et al. 2013; Chen et al. 2019; Qiu et al. 2019). Tri12, a predicted 14-membrane-spanning domain MFS transporter, localizes to small motile vesicles, larger stationary vacuoles, and motile vesicles, likely dynamically interacting with toxisomes. Tri12-containing vesicles may accumulate or transfer DON to the vacuole and eventually export DON from *F. graminearum* cells (Alexander et al. 1999; Menke et al. 2012, 2013; Boenisch et al. 2017). *F. graminearum* class I myosin FgMyo1 interacts with Tri1 and actin to promote the formation of the toxisome (Tang et al. 2018). Inhibition of FgMyo1 and actin polymerization by phenamacril (JS399-19, a novel cyanoacrylate fungicide) and latrunculin A, respectively (Zhang et al. 2015; Tang et al. 2018), reduce toxisome formation and DON biosynthesis. These results suggest that the FgMyo1-actin cytoskeleton system is important for the organization of the toxisome (Chen et al. 2019).

Factors inducing DON production and mechanisms underlying the regulation of DON production

F. graminearum infection causes environmental changes, including nutrition, pH, and oxidative stress that are related to the induction of DON production (Ponts 2015; Chen et al. 2019). Significantly high levels of DON production induced by sucrose, 1-kestose and nystose were observed in *F. graminearum* (Jiao et al. 2008). CreA (Mig1 in yeast), the global regulator of carbon catabolite repression, negatively regulates the expression of genes required for utilizing carbon sources (Fernandez et al. 2014). Predicted binding sites of FgCreA are present in promoters of *TRI1, TRI3-TRI8, TRI10, TRI12,* and *TRI101* (Hou and Wang 2018). Nevertheless, the exact roles of FgCreA in the regulation of DON biosynthesis are still unknown. Sucrose is the main carbon source transported from source to sink via highly specialized cells in the phloem vascular system (Xu et al. 2020) colonized by *F. graminearum* (Brown et al. 2010). Therefore, *F. graminearum* may hijack host sucrose transport pathways to facilitate its systemic infection by both utilization of host carbon sources and induction of DON biosynthesis.

Several nitrogen sources such as L-arginine, putrescine, agmatine, and guanine can stimulate DON production (Gardiner et al. 2009a). These compounds are either precursors or products in polyamine biosynthetic pathways. Plant polyamines are not only related to the generation of plant defense-related hydrogen peroxide and hydroxycinnamic acid amides, but are also involved in crosstalk with plant hormonal and signaling pathways such as salicylic acid (SA), abscisic acid (ABA), calcium, and nitric oxide (NO) (Gerlin et al. 2021). *F. graminearum* infection activates polyamine biosynthetic pathways and putrescine production in wheat heads, which further stimulates the biosynthesis of DON (Gardiner et al. 2010). Thus, *F. graminearum* appears to hijack wheat defense-related polyamines to produce virulence-associated DON and cause infection in plant. DON biosynthesis is regulated by FgAreA, a global regulator of nitrogen metabolism (Hou et al. 2015). FgAreA is translocated into the nucleus under nitrogen starvation conditions or in the presence of putrescine (Ma et al. 2021). Deletion of *FgAreA* suppresses the expression of *TRI5, TRI6,* and *TRI10*, and reduces DON production under the stimulation of arginine. FgAreA interacts with Tri10 for the transcriptional regulation of *TRI* genes (Hou et al. 2015). A recent study showed that FgAreA binds to the promoter regions of *TRI* genes to rearrange the nucleosome array. The exposure of nucleosome-free regions subsequently facilitates the deposition of histone H2B monoubiquitination (H2B ub1) and histone 3 lysine 4 di- and trimethylations (H3K4 me2/3) on *TRI* genes, which further activates the expression of *TRI* genes and promotes DON biosynthesis (Ma et al. 2021).

A low extracellular pH was reported to be a prerequisite for DON production in in vitro cultures of *F. graminearum* (Gardiner et al. 2009b; Merhej et al. 2010). Acidification induces the expression of *TRI4, TRI5, TRI6, TRI10,* and *TRI101*, while neutral growth PH induces neither the expression of *TRI* genes nor DON production

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(Merhej et al. 2010). Fungal transcription factor PacC is the key regulator that facilitates extra-cellular pH adaptation. Deletion of the *PacC* homolog *FgPac1* showed an earlier *TRI* gene induction and DON production under acidic pH conditions. Constitutive expression of the dominant allele *FgPac1^c* (truncated FgPac1, 1–490 amino acids) strongly repressed the expression of *TRI* genes (Merhej et al. 2011a). A total of 14 putative binding sites of FgPac1 were identified in the promoter region of *TRI* genes (Merhej et al. 2011b). However, the exact role of FgPac1 in the regulation of DON production still needs to be investigated. A recent study demonstrated that *F. graminearum* infection induces host to form an alkaline environment, under which the pH-dependent transcription factor FgPacC undergoes a proteolytic cleavage into the functional isoform named FgPacC30 (Gu et al. 2022).

Infection of a plant by phytopathogenic fungi induces a burst of H_2O_2, which is toxic to fungal pathogens and plays a critical role in plant defense signaling (Lehmann et al. 2015). DON production is induced by exogenous H_2O_2 in in vitro cultures (Ponts et al. 2006). During infection, defense-related H_2O_2 generated in plants stimulates the biosynthesis of DON. In addition, an improper fungicide dosage induces DON production, likely by stimulating the generation of H_2O_2. Treatment with prothioconazole induces a rapid hyperinduction of H_2O_2 that is required for DON production in *F. graminearum* (Audenaert et al. 2010). The transcription factor FgSkn7 is responsible for H_2O_2-induced *TRI* gene expression (Jiang et al. 2015). The promoters of multiple *TRI* genes, including *TRI5–TRI10, TRI12, TRI14,* and *TRI10*1, contain putative FgSkn7-binding elements (Jiang et al. 2015).

DON production is not only affected by various environmental and plant factors but also regulated by intracellular signaling and epigenetic mechanism. Whereas deletion of *PKA* or *FgFAC1* in the cAMP-PKA pathway reduces the biosynthesis of DON, the *pde* and *pkr* deletion mutants had an increased DON production (Jiang et al. 2016; Li et al. 2018; Yin et al. 2018). As an associated protein of FgFac1, FgCap1 is subject to feedback regulation mediated by Tri6 during DON production (Yin et al. 2018). Disruption of any one of the three MAPK signaling pathways or their downstream transcription factors results in a defect in DON production. Epigenetic regulation, including heterochromatin, histone methylation, and acetylation, are involved in the regulation of DON production (Ponts 2015; Chen et al. 2019). Deletion of the heterochromatin protein Hep1 represses the expression of *TRI5* and *TRI6* and consequently reduces DON production (Reyes-Dominguez et al. 2012). Deletion of *HEP1* reduced the enrichment of the H3K9me3 heterochromatic mark in the promoters of *TRI5* and *TRI6* (Reyes-Dominguez et al. 2012). Kmt6, the putative histone H3 lysine 27 methylation (H3K27me) methyltransferase, is responsible for transcriptional suppression of genes involved in the biosynthesis of mycotoxins, pigments, and other secondary metabolites, including *TRI4, TRI5,* and *TRI11* (Connolly et al. 2013). FgSet1-mediated H3K4me was reported to activate the expression of eight *TRI* genes (*TRI3–TRI6, TRI9–TRI12*) (Liu et al. 2015). Histone acetyltransferases FgGcn5, Elp3, and FgSas3 are involved in the activation of expression of *TRI* genes and DON production (Lee et al. 2014; Chen et al. 2018; Kong et al. 2018). Deletion of the histone deacetylase gene *HDF1* results in a significant reduction in DON production and virulence in *F. graminearum* (Li et al. 2011). Moreover, Fng1 and Fng3, two Inhibitor of Growth (ING) proteins associated with histone acetyltransferase (HAT) and histone deacetylase (HDAC) complexes, are important for DON production (Jiang et al. 2020b; Xu et al. 2022a).

Roles of *F. graminearum*-secreted enzymes and effectors in facilitating wheat infection by the pathogen

Secreted enzymes and proteins

Fungi secrete a variety of proteins, including cell wall-degrading enzymes (CWDEs), proteases, lipases, oxidoreductases, and effectors into extracellular milieu to benefit their survival. More than 500 CWDEs have been identified in *F. graminearum* (Zhao et al. 2014). Some important secreted pathogenicity factors of *F. graminearum* were exhibited in Fig. 2. Transcriptome analysis showed that a large number of CWDE-coding genes are upregulated during *F. graminearum* infection (Zhang et al. 2012; Cao et al. 2021). Cytological observation of *F. graminearum*-infected wheat spikes using enzyme-gold and immune-gold labeling techniques showed that the cell wall components such as cellulose, xylan, and pectin were degraded, likely mediated by CWDEs secreted by *F. graminearum* (Wanjiru et al. 2002; Kang et al. 2007). *F. graminearum*-secreted CWDEs macerate plant tissues to liberate nutrients for the growth and development of the pathogen. A comparative transcriptome study of symptomless and symptomatic wheat tissues infected by *F. graminearum* revealed that CWDE-encoding genes were highly induced in both symptomless and symptomatic wheat tissues, suggesting their important roles in different infection stages (Brown et al. 2017). The pectin methylesterase PME cooperates with polygalacturonase (PG) to degrade highly methyl-esterified pectin and promote the infection (Sella et al. 2016). *F. graminearum*-generated endo-polygalacturonase Pg and xylanase Xyr1 share a synergistic role during plant infection. The *pg xyr1* double deletion mutants but not the single mutants were
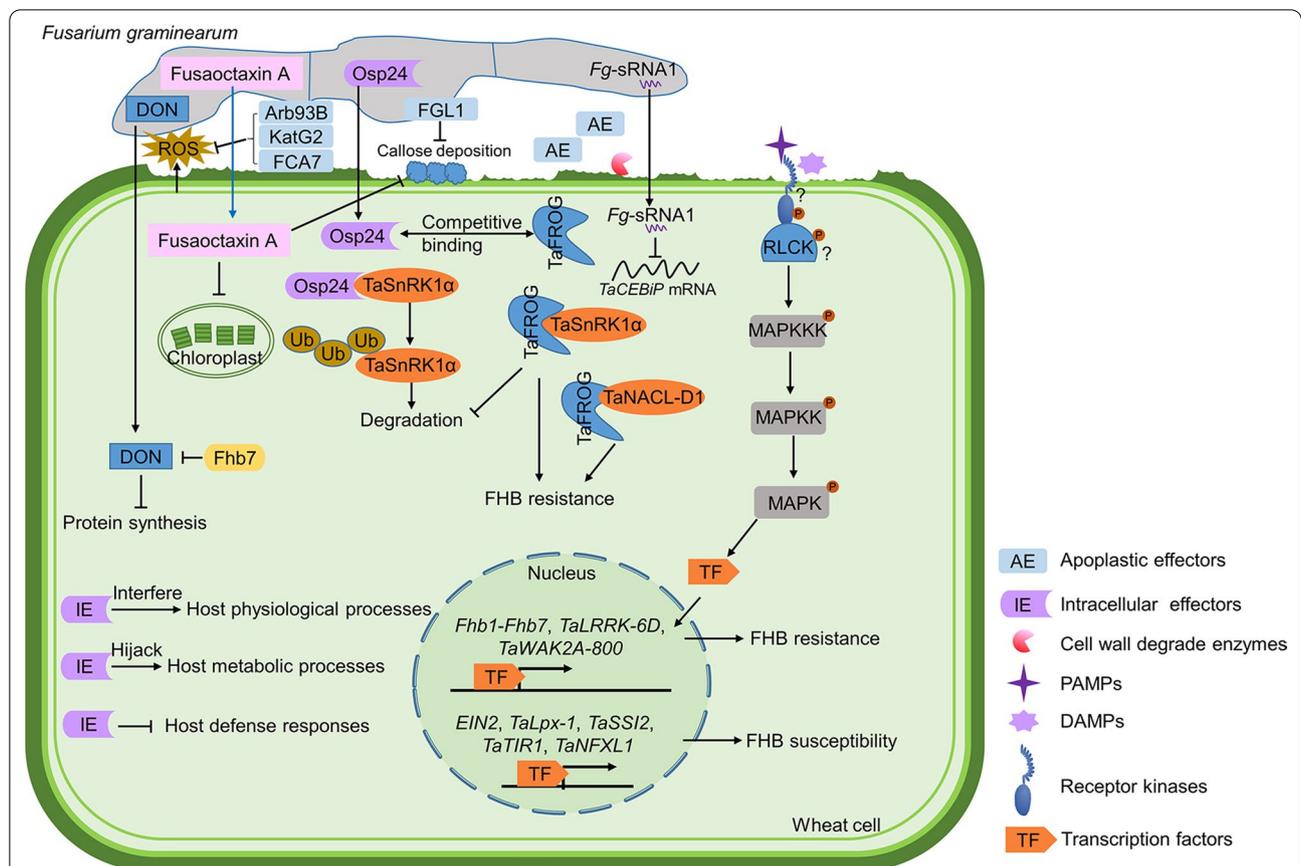
Fig. 2 Mode of action of *Fusarium graminearum*-secreted pathogenicity factors and FHB resistance and susceptibility genes in wheat during *F. graminearum*-wheat interaction. *F. graminearum* secretes cell wall-degrading enzymes (CWDEs) such as polygalacturonases and xylanases to degrade wheat cell walls. The apoplastic effector (AE) FGL1 suppresses callose deposition. *F. graminearum* exo-1,5-a-L-arabinanase Arb93B and the putative catalase-peroxidase KatG2 and FCA7 contribute to fungal virulence by suppressing host ROS generation. The orphan secreted protein Osp24 in *F. graminearum* functions as a cytoplasmic effector targeting host defense-related TaSnRK1α for degradation and is important for pathogenicity. The sRNA effector *Fg*-sRNA1 contributes to virulence by silencing wheat defense-related *TaCEBiP*. Fungal toxin DON inhibits protein biosynthesis by binding to the ribosome. DON also affects programmed cell death (PCD) of plant cells in a concentration-dependent manner. The fungal toxin Fusaoctaxin A changes the subcellular localization of chloroplasts in the coleoptile cells and prevents callose accumulation in plasmodesmata during pathogen infection, facilitating the cell-to-cell invasion of *F. graminearum* in wheat tissues. To combat *F. graminearum*, the DON response wheat orphan and defense-related protein TaFROG competes with Osp24 to interact with TaSnRK1α, preventing TaSnRK1α degradation mediated by the ubiquitin-26S proteasome system. TaFROG also interacts with the FHB resistance-related NAC-like transcription factor TaNACL-D1. Wheat FHB resistance genes *Fhb1*–*Fhb7* and pattern-triggered immunity (PTI) components, such as *TaLRRK-6D* and *TaWAK2A-800*, confer resistance to FHB. *Fhb7* encodes a glutathione *S*-transferase which detoxifies multiple trichothecene mycotoxins, whereas the wheat ethylene receptor gene *EIN2*, the 9-lipoxygenase-coding gene *TaLpx-1*, the stearoyl-acyl carrier protein fatty acid desaturase gene *TaSSI2*, the auxin receptor gene *TaTIR1*, and the DON-induced transcription factor gene *TaNFXL1* contribute to wheat susceptibility to FHB

significantly reduced in virulence (Paccanaro et al. 2017). ROS (reactive oxygen species) generated by the host is suppressed by *F. graminearum*- secreted exo-1,5-a-L-arabinanase Arb93B (Hao et al. 2019). The xylanase gene *XylA* derived from *F. graminearum* is involved in the degradation of D-xylose, the main component of cereal plant cell walls (Tini et al. 2020). Functional redundancy is a common property of CWDEs in plant pathogenic fungi (Xu et al. 2018). Although transcription levels of five of the seven feruloyl esterase-coding

genes of *F. graminearum* are increased during infection of plant, deletion of them individually showed no obvious reduction in pathogenicity (Balcerzak et al. 2012). In addition to CWDEs, the tomatinase-like enzyme FgTom, KP4-like proteins, the putative catalase-peroxidase KatG2 and Fca7, and cerato-platanins were verified to be involved in *F. graminearum*-host interactions to some extent (Voigt et al. 2005; Carere et al. 2017; Lee et al. 2018; Guo et al. 2019; Lu and Faris 2019; Quarantin et al. 2019b; Eranthodi et al. 2022).

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Effectors

Generally, effectors are defined as pathogen-secreted factors that alter the interaction between pathogen and host (Varden et al. 2017; Tariqjaveed et al. 2021). To suppress host defense, plant pathogens secrete a variety of effectors into the plant apoplast or directly into plant cells to manipulate plant physiology and immunity system and suppress host defense responses (Wang et al. 2022). The hemibiotrophic lifestyle of *F. graminearum* suggests that this pathogen may be equipped with a broad arsenal of effectors (Gorash et al. 2021). Indeed, a recent study has identified multiple candidate effector genes and a total of 357 effectors in *F. graminearum*, which constitute the core effectome of the pathogen (Rocher et al. 2022). The lipase Fgl1 is secreted by *F. graminearum* to suppress the immunity-related callose deposition of the host (Blümke et al. 2014). An orphan secreted protein Osp24 in *F. graminearum* functions as a cytoplasmic effector targeting TaSnRK1α for degradation and is important for the pathogenicity of *F. graminearum* (Fig. 2; Jiang et al. 2020a). Three secreted protein-encoded genes, *FGSG_01831* (Accession number in the comprehensive reference annotation YL1 for PH-1: *FG1G27550*), *FGSG_03599* (*FG2G27040*), and *FGSG_12160* (*FG1G38440*), were highly expressed in *F. graminearum* when the pathogen infects wheat tissues; two of them suppressed Bax-induced cell death, while all of them interfered with chitin-triggered ROS generation; nevertheless, the deletion mutants of each of these effector genes were normal in pathogenicity (Hao et al. 2020a).

In recent years, fungal nonproteinaceous effectors, such as small RNA (sRNA) effectors and secondary metabolites (chemical effectors), generate a paradigm shift in interactions between plants and phytopathogenic fungi (Collemare et al. 2019). A *F. graminearum* sRNA, *Fg*-sRNA1, promotes pathogen infection by silencing wheat defense-related *TaCEBiP* (Jian and Liang 2019). Two nonribosomal octapeptides, fusaoctaxin A and B biosynthesized by the gene cluster *fg3_54*, were identified as virulence factors of *F. graminearum* (Jia et al. 2019; Tang et al. 2021). Fusaoctaxin A alters the subcellular localization of chloroplasts in the coleoptile cells and prevents callose accumulation in plasmodesmata during pathogen infection, which facilitates the cell-to-cell invasion of *F. graminearum* in wheat tissues (Jia et al. 2019). In contrast, Fusaoctaxin B contributes to virulence by disrupting the normal chloroplast distribution (Tang et al. 2021).

Wheat components involved in interactions with *F. graminearum*

Innate immunity confers wheat resistance to *F. graminearum*

Fungal infection usually activates plant immune responses such as the influx of calcium ion (Ca^{2+}), ROS burst, transcriptional reprogramming, antimicrobial substance production, and callose deposition (Xu et al. 2022b). Transcriptome and proteome profiling are efficient approaches for the identification of wheat genes that are associated with FHB resistance (Kazan and Gardiner 2018; Pan et al. 2018; Liu et al., 2019). Two leucine-rich repeat-RKs and two RKs with lectin domain-coding genes have been identified by transcriptome sequencing of three FHB-resistant wheat genotypes (Nyubai, Wuhan 1, and HC374) and one susceptible wheat genotype (Shaw) (Pan et al. 2018). The leucine-rich receptor-like kinase gene *TaLRRK-6D* is induced in wheat by DON treatment during the early stage of *F. graminearum* infection. Silencing of *TaLRRK-6D* compromises wheat resistance to *F. graminearum* by suppressing the expression of salicylic acid signaling genes, including *ICS1*, *PAL*, *NPR1*, *NPR3-like,* and *NPR4* (Thapa et al. 2018). The transcription level of wheat wall-associated kinase gene *TaWAK2A-800* is increased when plants are treated with chitin or infected by *F. graminearum.* Defense-related genes such as *TaCERK1*, *TaRLCK1B,* and *TaMPK3* are down-regulated in *TaWAK2A-800* RNAi wheat lines that are susceptible to *F. graminearum* (Guo et al. 2021).

FHB resistance genes identified by quantitative trait loci (QTL) mapping

FHB resistance in wheat is inherited quantitatively and controlled by either major or minor QTL (Waldron et al. 1999; Semagn et al. 2007). More than 600 QTL distributed among all 21 chromosomes in wheat have been detected by linkage mapping or association mapping (Liu et al. 2009; Ma et al. 2020; Zheng et al. 2021). However, only seven FHB-resistant QTL (*Fhb1–Fhb7*) have been formally designated (Guo et al. 2015; Singh et al. 2016; Hao et al. 2020b).

To date, two FHB resistance genes *Fhb1* and *Fhb7* have been cloned by QTL mapping. Rawat et al. (2016) reported the map-based cloning of *Fhb1* from Sumai 3 and showed that the pore-forming toxin-like gene *PFT* is responsible for *Fhb1*-mediated resistance through mutation analysis, gene silencing, and overexpression. In two recent studies, Su et al. (2019) and Li et al. (2019) independently identified a histidine-rich calcium-binding gene (*TaHRC* or *His^R*) adjacent to PFT as a new Fhb1 candidate. Su et al. (2019) demonstrated that *TaHRC* is a susceptibility gene, a deletion spanning the start codon

of this gene results in FHB resistance. Li et al. (2019) proposed that His^R is a gain-of-function mutation, and that the newly generated protein enhances wheat immunity. The contrasting functions of *Fhb1* suggest the complexity of wheat-*F. graminearum* interaction. Cloning of *Fhb1* has contributed substantially toward the improvement of breeding wheat with FHB resistance worldwide. *Fhb7* was cloned from *Thinopyrum elongatum,* a species used in wheat distant hybridization breeding (Wang et al. 2020a). *Fhb7* encodes a glutathione *S*-transferase which detoxifies trichothecene and overexpression of *Fhb7* in wheat variety KN199 enhanced the FHB resistance of wheat (Wang et al. 2020a).

Effector-based identification of wheat components against *F. graminearum*

In-depth knowledge of pathogen-host interactions shines a light on the development of breeding strategies (Li et al. 2021). With the Osp24 as a bait, TaSnRK1α was identified as an interacting protein of Osp24. Overexpression and silencing of *TaSnRK1α* enhanced and attenuated wheat resistance to FHB, respectively (Jiang et al. 2020a). TaSnRK1α was previously identified as an interacting protein of a DON response wheat orphan protein TaFROG, which is associated with FHB resistance (Perochon et al. 2015). Osp24 and TaFROG interacted competitively with the same C-terminal region of TaSnRK1α (267–499 aa). Overexpression of TaFROG may improve FHB resistance by preventing TaSnRK1α degradation mediated by the ubiquitin-26S proteasome system (Jiang et al. 2020a). Besides, TaFROG also interacts with the wheat NAC-like transcription factor TaNacL-D1. Overexpression of *TaNACL-D1* enhances wheat resistance to FHB (Perochon et al. 2019). Therefore, effectors discovered in the *F. graminearum*-wheat interaction may direct the identification of resistant and susceptible components that can be utilized to develop FHB resistance in wheat.

Susceptibility of wheat to FHB

Susceptibility genes in plants are negative regulators of plant immunity or the genes hijacked by pathogens to promote their colonization and growth (van Schie and Takken 2014). A susceptibility QTL was identified in the long arm of chromosome 2A by QTL-mapping (Garvin et al. 2009). A type II FHB susceptibility factor was identified in wheat chromosome 4D by point-inoculating wheat lines possessing barley chromosome introgressions. Wheat lines del4DS-3 and del4DS-1, which contain larger deletions of chromosome 4D, confer resistance to FHB, suggesting the susceptibility factor exists in this deletion region (Hales et al. 2020). Silencing of *TaLpx-1*, the wheat homolog of Arabidopsis *LOX1*

and *LOX5*, enhances wheat resistance to FHB, demonstrating that *TaLpx-1* acts as a susceptibility gene during the *F. graminearum*-wheat interaction (Nalam et al. 2015). Silencing of ethylene receptor gene *EIN2* in wheat enhances FHB resistance and reduces DON content in the inoculated heads (Chen et al. 2009). Silencing of the wheat stearoyl-acyl carrier protein fatty acid desaturase gene *TaSSI2* enhances FHB resistance by depressing the SA signaling pathway in wheat (Hu et al. 2018). In addition, RNAi-mediated knockdown of the auxin receptor gene *TaTIR1* enhances wheat FHB resistance (Su et al. 2021). Silencing or knockout of a DON-induced transcription factor *TaNFXL1* enhances wheat resistance to FHB, suggesting that *TaNFXL1* is a susceptibility gene during *F. graminearum*-wheat interaction (Brauer et al. 2020). Counteracting these susceptibility factors and genes may contribute to the future development of FHB-resistant wheat varieties.

Conclusions and perspectives
F. graminearum genes as potential targets for HIGS- and SIGS-based disease control

To date, hundreds of genes important for fungal development, pathogenesis, and DON production have been widely identified in *F. graminearum*. RNA interference of those genes may inhibit the growth and infection of *F. graminearum*, which potentially can be used for FHB control. HIGS (host-induced gene silencing) and SIGS (spray-induced gene silencing) have been developed to silence *F. graminearum* genes including *CHS3b*, *FgPP1*, *FgSGE1*, *FgSTE12*, and *CYP51* (Cheng et al. 2015; Koch et al. 2016; Wang et al. 2020b). Further functional characterization of *F. graminearum* genes will lay the foundation for the generation of HIGS transgenic wheat and the development of nucleic acid pesticides.

Interfering with the signaling sensing of *F. graminearum* to block the transitions between saprophytic and pathogenic growth

Fungicides (including benzimidazoles, triazoles, carboximides, and JS399-19) strongly inhibited the growth of *F. graminearum* and tended to be efficient strategies for the control of FHB in the field (Zhang et al. 2015; Zhou et al. 2020). However, *F. graminearum* frequently developed resistance against these fungicides under selection pressure. As a hemibiotrophic pathogen, *F. graminearum* has both saprophytic and pathogenic growth in its life cycle. Instead of killing the fungus, a potential alternative strategy is blocking the initiation of infection without inhibiting saprophytic growth. Host signals sensing mediates the transitions from saprophytic growth to pathogenic growth phases, and is also required for the activation of DON biosynthesis. Wheat anthers are rich

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in various nutrients and have stimulating compounds to stimulate the virulence of *F. graminearum* (Jiang et al. 2019). Moreover, plant-derived polyamines act as a cue to trigger DON biosynthesis (Gardiner et al. 2010). Intracellular signaling pathways are coordinately involved in responses to various plant signals recognized by a variety of *F. graminearum* receptors. Reducing wheat-derived cues to weaken the stimulation from the host plant or interfering with the signaling sensing by inhibiting the function of *F. graminearum*-secreted receptors (or the downstream signaling) may be useful approaches to improve FHB resistance.

F. graminearum-secreted protein as bait to capture and identify resistance and susceptibility genes in wheat

A large number of *in planta*-specific upregulation secreted protein-encoded genes were identified from the omics studies, although only a few of them have been functionally characterized. These secreted proteins may enter the plant cells to modulate the functions of plant genes. Whereas some of them interact with resistance genes to suppress plant defense responses (Jiang et al. 2020a), others may target susceptibility genes to facilitate the invasive growth of *F. graminearum* (Fig. 2). Recently, the full-length transcriptome annotation of *F. graminearum* was generated (Lu et al. 2022), which facilitates the comprehensive identification of additional secreted proteins. With more secreted proteins being functionally characterized in *F. graminearum*, it will be possible to identify their host targets and even the exact interaction sites. CRISPR/Cas9 system has provided an efficient tool for generating site-specific mutations in genes of interest (Grutzner et al. 2021). Disrupting the targeted gene of *F. graminearum* by gene editing will likely enhance the FHB resistance of wheat. In contrast, disrupting the susceptibility genes may interfere with the compatibility between the host and the pathogens and consequently provide broad-spectrum disease resistance (Zaidi et al. 2018). The overexpression of plant resistance proteins often comes with a trade-off with growth, but gene editing of the pathogen-targeting sites may not affect the biological function of host genes and will not produce significant deleterious effects on the yield and quality traits of wheat.

Use of other pathosystems to identify genes for developing resistance against *F. graminearum*

Arabidopsis and *Brachypodium distachyon* are two model plants that have been used to study *F. graminearum*-plant interactions (Chen et al. 2009; Peraldi et al. 2011; Brewer and Hammond-Kosack 2015). Multiple genes related to Arabidopsis resistance and susceptibility to *F. graminearum* have been identified in the past 10 years (Brewer and Hammond-Kosack 2015). In addition, *F.* *graminearum* can infect intact foliar tissues of the monocotyledonous model species *B. distachyon*, indicating that *B. distachyon* is also a valuable model plant for the study of FHB (Peraldi et al. 2011; Brewer and Hammond-Kosack 2015). Further investigation of the interactions between these two model plants with *F. graminearum* may provide new clues to study the wheat-*F. graminearum* interaction and facilitate the development of strategies to improve wheat resistance against *F. graminearum*.

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