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Update on the state of research to manage *Fusarium* head blight

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ABSTRACT

Fusarium head blight (FHB) is one of the most devastating diseases of cereal crops, causing severe reduction in yield and quality of grain worldwide. In the United States, the major causal agent of FHB is the mycotoxigenic fungus, *Fusarium graminearum*. The contamination of grain with mycotoxins, including deoxynivalenol and zearalenone, is a particularly serious concern due to its impact on the health of humans and livestock. For the past few decades, multidisciplinary studies have been conducted on management strategies designed to reduce the losses caused by FHB. However, effective management is still challenging due to the emergence of fungicide-tolerant strains of *F. graminearum* and the lack of highly resistant wheat and barley cultivars. This review presents multidisciplinary approaches that incorporate advances in genomics, genetic-engineering, new fungicide chemistries, applied biocontrol, and consideration of the disease cycle for management of FHB.

1. Introduction

Fusarium head blight (FHB) is one of the most challenging fungal diseases that affect cereal crops worldwide. The disease reduces grain yield and results in toxic contaminants that render grain inedible. Several *Fusarium* species are associated with FHB (Dill-Macky and Jones, 2000; Ma et al., 2020); however, the most prevalent causal agents belong to the *Fusarium graminearum* species complex (FGSC). Among the seventeen phylogenetically distinct subgroups belonging to the FGSC, the predominant species causing FHB in the United States is *F. graminearum* (de Chaves et al., 2022; Del Ponte et al., 2022; Gale et al., 2007), which causes FHB in cereal crops, including wheat, barley, rice, corn, and oats. In the United States, FHB has been the greatest threat to cereal crops for multiple decades (Bai and Shaner, 1994; Dill-Macky, 1996; McMullen et al., 1997; McMullen et al., 2008; Powell and Vujanovic, 2021). The outbreaks date back to 1917, when they were reported in 31 states with an estimated yield loss of 288,000 metric tons of wheat (Atanasoff, 1920; McMullen et al., 1997). From 1993 to 2014, wheat farmers in the United States lost $17 billion worth of wheat due to FHB (Ma et al., 2020). An outbreak in the Southeastern United States in 2003 resulted in severe economic losses to wheat growers, primarily in Maryland, North Carolina, and Virginia, with a loss of over $13 million (Cowger and Sutton, 2005). In 2010, parts of Ohio reported a 60% incidence of FHB in wheat fields, which is typical of fields worldwide when environmental conditions are conducive to disease (McMullen et al., 2012). Although significant preventative measures have been developed and implemented for the control of *F. graminearum,* FHB remains a problematic disease to cereal farmers across the globe as the effectiveness of control measures varies depending upon weather conditions.

In wheat and barley, *F. graminearum* primarily affects the inflorescence, and the initial symptoms appear shortly after flowering. Infection is initiated when airborne ascospores (sexual spores) and conidia (asexual spores) are deposited on florets, primarily by wind dispersal (Fig. 1). These spores are released from colonized crop residues (Bai and Shaner, 2004; Imboden et al., 2018) and other infected hosts (Fulcher et al., 2019a). *F. graminearum* also causes stalk rot in maize, as well as root rot in other crops, including wheat, maize, and soybean (Kang et al., 2019; Li et al., 2016a; Reid et al., 2001; Wang et al., 2015a). *F. graminearum* infects wheat and barley during anthesis through the developing florets, and after initial infection, the fungus colonizes internal tissues of the developing grains with hyphae. The initial

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symptoms of the infection are dark-brown areas on the glumes of infected florets, which subsequently lead to the bleaching of the entire floret. The infection spreads both internally and externally to adjacent florets, across the entire head, and down the rachis through the stalk (Boenisch and Schäfer, 2011; Guenther and Trail, 2005; Jansen et al., 2005). As the symptoms progress, the infected kernels appear shriveled and bleached and are commonly known as tombstones (McMullen et al., 1997). Environmental conditions significantly influence the initiation and severity of the disease, where high humidity (>90%) and moderate temperatures (59 to 86°F) favor the fungus and lead to more severe incidences of FHB in the field. At the end of the growing season, *F. graminearum* overwinters on colonized crop residues, where the next spring fruiting bodies develop under favorable environmental conditions (Dill-Macky and Jones, 2000; Naef and Défago, 2006), and the cycle continues.

F. graminearum contaminates grains with mycotoxins, including deoxynivalenol (DON), nivalenol, and zearalenone. The amount of mycotoxins in the infected grains varies depending on several factors, including weather conditions, preharvest control strategies, time of harvest, and resistance level of the cultivar (Mielniczuk and Skwaryło-Bednarz, 2020). The resulting mycotoxins in the grains after *F. graminearum* infection not only affect nutritional quality, but also endanger the health of humans and livestock through the consumption of mycotoxin contaminated food (Huff et al., 1981; Malekinejad et al., 2007; Mudge et al., 2006; Rotter et al., 1996). In addition, most of the barley grown in the United States is used for malting by the brewing industry, and *F. graminearum* infection of barley leads to gushing of bottled beer caused by contamination with fungal hydrophobins during the malting process (Denschlag et al., 2012).

FHB is a difficult disease to control. Extensive research has been conducted on developing management strategies to reduce the losses caused by FHB. Adequate control of FHB cannot be accomplished by a single approach. Currently, integrated disease management is recommended through combining fungicides with tolerant crop varieties, and crop rotation to reduce inoculum from susceptible crops (Amarasinghe et al., 2013; McMullen et al., 2012; Willyerd et al., 2012). These practices manage the disease well in years where environmental conditions do not significantly favor the pathogen. However, in years where weather (cool temperatures and rain) favors the fungus, such strategies do not work. For the long term, new means of control must be innovated. While developing effective management, it is necessary to select tools that are stable, cost-effective, and eco-friendly. Above all, the chosen management strategy should prevent or reduce the development of resistant *F. graminearum* strains. In this review, we focus on the current management strategies and explore innovative directions for FHB management (Fig. 1). The genetics and chemistry of DON biosynthesis and its effects on plants, humans and animals are beyond the scope of this review, but have been presented elsewhere, including Chen et al. (2019), Cimbalo et al. (2020), Payros et al. (2016), Rocha et al. (2005), and Sumarah (2022).

2. FHB management strategies

2.1. Agricultural practices

Agricultural practices, including the selection of resistant cultivars, crop rotation, management of crop residues using tillage, irrigation, and applying efficient disease forecasting models, have proven successful in mitigating the incidence and spread of FHB (Fernando et al., 2021; McMullen et al., 2012; Wegulo et al., 2015). Hyphae of *F. graminearum*, overwintering on crop residues, produce fruiting bodies under favorable environmental conditions, and the ascospores discharged from these fruiting bodies serve as the major FHB inoculum, which can be minimized through the careful management of the residues (Blandino et al.,

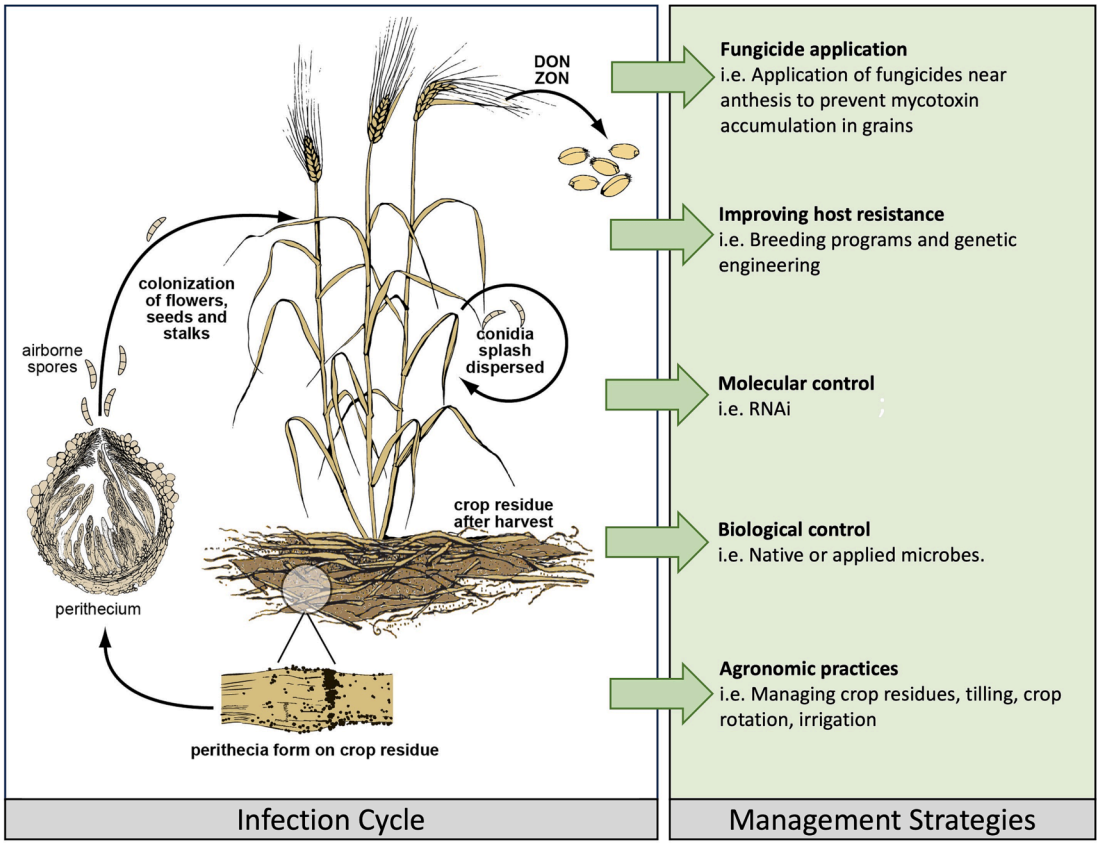

Fig. 1. FHB infection cycle and management strategies (Figure modified from Trail, 2009).

2010, 2012; Dill-Macky and Jones, 2000; Guenther et al., 2009; McMullen et al., 2012; Osborne and Stein, 2007). Therefore, tillage, which reduces large amounts of crop residue on the soil surface is effective in decreasing FHB incidence (Dill-Macky and Jones, 2000; Schaafsma et al., 2005). Crop rotation is also recommended for reducing FHB outbreaks, and rotating wheat or barley with a non-host crop species reduces the *F. graminearum* inoculum load in the field (Shah et al., 2018). Soybean is one of the crops most commonly recommended for rotation with wheat, barley, and maize to reduce the risk of disease development. However, studies have shown that *F. graminearum* can colonize soybean and become a source of inoculum (Chiotta et al., 2020; Kang et al., 2019). In addition to crop rotation, the management of non-cultivated plants such as weeds, including other grasses, is important in reducing the amount of inoculum in fields, as several common weeds within cereal crop rotations may serve as reservoir hosts for *F. graminearum* (Fulcher et al., 2019b; Suproniene et al., 2019). Studies have shown that crop rotations can significantly impact the microbiome of durum wheat, including encouraging beneficial species that can be used as biological control agents against pathogenic fungal species, emphasizing the importance of assessing microbial diversity as part of effective integrated management strategies (Vujanovic et al., 2012). Biological control of FHB and the host microbiome are discussed in section 2.4. There are limitations to managing FHB outbreaks through agricultural practices, especially when the climatic conditions are favorable for infection, so more effective strategies are needed to incorporate into the integrated FHB management program.

Recently, the addition of silica to the soil as a fertilizer has been shown to reduce FHB incidence and severity (Pazdiora et al., 2021; Sakr, 2021a), especially in combination with fungicide treatments (Pazdiora et al., 2022). Numerous studies have demonstrated the active involvement of silicon (Si) in mediating host resistance against fungal pathogens, including *Blumeria graminis* (Bélanger et al., 2003; Rémus-Borel et al., 2005), *Bipolaris sorokiniana* (Domiciano et al., 2013), *Drechslera tritici-repentis* (Dorneles et al., 2017), *F. culmorum, F. verticillioides, F. solani, F. equiseti* (Sakr, 2021a; Sakr and Kurdali, 2022) and *Magnaporthe grisea* (Rodrigues et al., 2004; Rodrigues et al., 2005). Plants absorb silicic acid via the roots, then translocate it to the shoots, where it is polymerized into silica (Ma and Yamaji, 2006; Mayland et al., 1991). A field study demonstrated the effect of amending soil with calcium silicate in reducing FHB severity in wheat (Pazdiora et al., 2021). The effect of silicon applications to roots versus leaves in reducing FHB incidence and severity was compared, and the results showed that neither treatment reduced disease incidence nor severity during the initial infection stage. However, both aspects were significantly reduced two weeks after initial infection, revealing that successful reduction of FHB requires a minimum concentration of silica to accumulate in the host tissues to modulate defense responses (Sakr, 2021b). An *in vitro* bioassay on wheat showed that *Fusarium* spp. can proliferate on the plant surface, regardless of silica application, indicating that silica may not act directly on the fungus (Sakr, 2022). Yobo et al. (2019) analyzed the efficacy of applying potassium silicate under greenhouse conditions; however, their results revealed no significant reduction in FHB severity in wheat. There is some evidence that the interaction of *F. graminearum* with silica treated plants enhances disease. Two recent publications present data that silica amendments were associated with disease reduction in wheat. However, it was also noted in these reports that applications of silica did not reduce hyphal growth, and that mycotoxin contamination in kernels was more severe than in unamended controls in susceptible cultivars (Pazdiora et al., 2022; Sakr, 2022). For clarity, more research efforts are needed to uncover the association of silica to FHB.

2.2. Fungicides

Fungicides are the primary means of controlling FHB in the United States and many areas of the world. However, high FHB disease pressure in fields, usually brought on by conducive weather conditions, can result in greater than 60% disease incidence even in the presence of fungicide applications (González-Domínguez et al., 2021; Haidukowski et al., 2005; Lehoczki-Krsjak et al., 2010; Singh et al., 2021). Several other factors influence the efficacy of fungicide applications, including the severity of the infection, the timing of application and the type of fungicide, the resistance level of cultivars, and the tolerance of the pathogen to the chemicals (Bolanos-Carriel et al., 2020; Mesterházy et al., 2011). In wheat, fungicides are applied during a short window of time, coinciding approximately with anthesis, when the fungus initiates infection that will result in grain contamination (Caldwell et al., 2017; Freije and Wise, 2015). However, the timing of fungicide application for successful control can be up to 11 days after anthesis to avoid DON accumulation in the seed (Freije and Wise, 2015). In barley, fungicide timing is dependent on whether the cultivar is open-flower or closed-flower, where closed-flowering cultivars can benefit from later applications due to delayed access of spores to floral parts (Yoshida et al., 2008). Additionally, the use of a combination of multiple fungicides during the growing season has been shown to be more effective in controlling FHB for the full season (Barro et al., 2021; Caldwell et al., 2017; Friskop et al., 2023; Haidukowski et al., 2005).

In the United States, the most commonly used fungicides to control FHB are the azoles, which target the ergosterol biosynthetic pathway, specifically the cytochrome P450 sterol 14α-demethylase (CYP51), leading to instability of cell membranes (Amarasinghe et al., 2013; Anderson et al., 2020; Caldwell et al., 2017; Chen and Zhou, 2009; Freije and Wise, 2015; Haidukowski et al., 2005; Paul et al., 2018). A widely used fungicide chemistry registered for control of FHB is the succinate dehydrogenase inhibitors (SDHIs), which inhibit the respiratory electron transport chain (Avenot and Michailides, 2010). The quinone outside inhibitors (QoI), such as the strobilurins, affect the mitochondrial cytochrome-bc complex, are found to be less effective than azole-based fungicides in controlling FHB (Bolanos-Carriel et al., 2020; Paul et al., 2018). A recent study reported that QoI can enhance mycotoxin synthesis by accelerating the production of acetyl-CoA, a substrate involved in the trichothecene biosynthetic pathway of *F. graminearum* (Duan et al., 2020).

Although a combination of fungicides and tolerant host varieties can provide stable control, there is growing concern for the development of fungicide resistance. For instance, the emergence of resistant *F. graminearum* isolates in field populations has been reported following the continuous use of triazoles (Anderson et al., 2020; Chen et al., 2021a). Zhao et al. (2022) observed that a single amino acid substitution (G443S) of the *CYP51A* gene in *F. graminearum* significantly reduced sensitivity to ergosterol biosynthesis inhibitors including tebuconazole and metconazole. Cross resistance can develop when the genes imparting resistance to one fungicide can provide tolerance to fungicides in other classes. An *in vitro* study exposing a field isolate to sublethal doses of tebuconazole yielded two resistant phenotypes, one developing azole-specific cross resistance, and the other developing multidrug resistance with increased tolerance to amine fungicides, as well as azoles. The study demonstrated the ability of *F. graminearum* to become resistant to multiple classes of fungicides in a short time due to exposure to a single fungicide (Becher et al., 2010). The development of multidrug resistance is linked to the activation of efflux transporters and has been reported in other phytopathogenic fungal species as well (Cheng et al., 2023; De Waard et al., 2006, Samaras et al., 2020; Vicentini et al., 2022). Recent evidence demonstrates the critical role of the plasma membrane localized H^+ antiporter, FgQdr2, as a drug efflux pump that confers multidrug resistance in *F. graminearum*. The activation of FgQdr2 has been shown to be involved in the efflux of multiple fungicides, and the absence of the FgQdr2 gene causes increased sensitivity to fungicides. The specific role of FgQdr2 in multidrug resistance is not known, but it has been suggested that the changes in the proton gradient and environmental chemical stress upregulate the FgQdr2 gene, resulting in resistance (Ma et al., 2022).

In two separate studies, transcriptomic analyses in *F. graminearum*

following azole fungicide applications revealed that genes of the ergosterol biosynthetic pathway were significantly upregulated, including those that are not the direct target of azoles (Becher et al., 2011; Liu et al., 2010). Additionally, ABC transporters, transcription factors, and genes involved in cellular metabolism were upregulated, indicating the potential of the fungus to efflux the fungicide through transporters and to generate more ergosterol to alleviate the impact of the fungicide. An interesting case study in *F. graminearum* reported how resistance to phenamacril, a cyanoacrylate fungicide that interferes with mycelial growth by targeting the myosin 1 gene, develops. Phenamacril was developed due to high resistance to the β-tubulin-specific antifungal agent, carbendazim, in strains in China, where carbendazim is commonly used to control FHB. However, in testing phenamacril in the lab, resistance developed multiple times in *F. graminearum* (Chen and Zhou, 2009; Zheng et al., 2014, 2015). Genetic studies have shown that resistance occurs due to point mutations in multiple, separate genes, each of which confers resistance to multiple fungicides on its own. For example, mutations in the myosin 5 and β-tubulin genes render resistance to the fungicides phenamacril and carbendazim, respectively (Liu et al., 2019, Zheng et al., 2014, 2015). A similar study assessed the development of resistance to the SDHI fungicide, pydiflumetofen, as well as the risk of cross-resistance between pydiflumetofen and other fungicides. Sequencing analysis and cross-resistance tests showed that resistance to SDHIs developed by mutations in the genes encoding the succinate dehydrogenase subunit without conferring resistance to fungicides such as tebuconazole and phenamacril (Sun et al., 2020). To achieve the sustainable management of crop diseases through chemical control, frequent introduction of chemistries with new modes of action is essential (Steinberg and Gurr, 2020).

Novel compounds for the control of fungi have been mined from a variety of organisms, including plants, lichens, fungi, and bacteria. Such specialized (secondary) metabolites have demonstrated their antifungal properties primarily *in vitro* (Annis et al., 2000; Bemvenuti et al., 2019; Chen et al., 2018a; Drakopoulos et al., 2020, 2019; Gao et al., 2016; Heidtmann-Bemvenuti et al., 2016; Kouassi et al., 2017; Schöneberg et al., 2018). Similarly, essential oils derived from plant sources have been shown *in vitro* to combat fungal pathogens (Chen et al., 2020; Delaquis et al., 2002; Ferreira et al., 2018; Hyldgaard et al., 2012; Kumar et al., 2016; Rao et al., 2019). Lichens have also been mined for novel antifungal compounds. The unique assortment of phenolic (aromatic) compounds such as depsides, depsidones, and dibenzenofurans produced by lichens possess a variety of biological activities (Calcott et al., 2018; Molnár and Farkas, 2010; Shrestha and St Clair, 2014). Several lichen compounds have been shown to affect mycotoxin biosynthesis in *Aspergillus* spp. and *F. graminearum* (Annis et al., 2000; Pani et al., 2016). Since some lichen compounds possess strong antioxidant activity (Fernández-Moriano et al., 2016; Kosanić, et al., 2011), they may lessen the oxidative stress that triggers mycotoxin biosynthesis (Audenaert et al., 2010; Grintzalis et al., 2014; Ponts et al., 2007, 2006, 2003; Reverberi et al., 2006), thus reducing mycotoxin accumulation. Although a large number of studies on natural compounds have shown their potential antifungal activity, many of these findings are limited to *in vitro* or greenhouse trials. The antifungal potential of these compounds must be tested *in planta* under field conditions to develop an effective antifungal commercial formulation that is easy to produce, has an affordable price, a long shelf life, and flexible application requirements.

2.3. Host resistance

Use of highly resistant cultivars would provide the most efficient means of reducing FHB outbreaks. FHB resistance in small grain cereals is classified into five types (Fernando et al., 2021; Foroud and Eudes, 2009; Mesterházy et al., 1999). Type I is defined as resistance to initial fungal infection, and type II resistance corresponds to the suppression of spread of FHB within the host plant, and resistance to trichothecene accumulation characterizes type III resistance (Buerstmayr et al., 2019; Lemmens et al., 2005; Mesterházy et al., 1999; Wang and Miller, 1988). Type IV is described as resistance to kernel infection rate (Fernando et al., 2021; Mesterházy et al., 1999), whereas type V resistance is described as the ability of the host plant to stop mycotoxin production by the fungus and convert it to non-toxic derivatives (Martin et al., 2017). In addition, the plant's phenotypic characteristics, including the height, spikelet density, and time of flowering, contribute to tolerance of FHB and is termed "passive resistance" (Mesterházy, 1995; Pritsch et al., 2000). Currently, the cultivars developed through conventional breeding programs are only moderately resistant. Development of highly resistant cultivars has proven challenging as FHB resistance is under complex polygenic control with only moderate heritability (Aviles et al., 2020).

Selected wheat cultivars with accumulated resistance have been used in wheat breeding programs to develop stronger resistance. Wheat accessions Sumai 3, Wangshuibai, and Nyu Bai are commonly used by breeders to develop resistant cultivars (Bai and Shaner, 2004; Ma et al., 2020). Sumai 3 and Wangshuibai originated in China, while Nyu Bai is a Japanese landrace (Bai and Shaner, 2004; Ma et al., 2020; Niwa et al., 2014; Zhou et al., 2004). Among these, Sumai 3 exhibits type I and II resistance, was developed from two moderately susceptible cultivars, and its descendants are used in most FHB resistance breeding programs worldwide.

In barley, *F. graminearum* shows limited internal spread from the rachis, thus rendering most barley varieties naturally type II resistant (Langevin et al., 2004). However, barley is highly susceptible to initial infection, with 2-row barley typically more resistant than 6-row barley (He et al., 2015). Wild relatives of barley have been screened for resistance to provide a reservoir of resistance genes for breeding (Bai and Shaner, 2004). However, wild *Hordeum* species are not more resistant to FHB than the cultivated varieties, which increases the difficulty of breeding fully resistant varieties.

Genetic mapping studies have shown that multiple quantitative trait loci (QTLs) are implicated in FHB resistance of wheat and barley, including resistance to mycotoxin accumulation. Over 500 QTLs related to FHB resistance have been reported in wheat (Buerstmayr et al., 2009; Buerstmayr et al., 2019; Chen et al., 2021c; Ma et al., 2020; Poudel et al., 2022; Song et al., 2022), however, more studies are required to validate the majority of these QTLs. The most widely studied QTLs are *Fhb1* and *Fhb7* (Wang et al., 2020). *Fhb1*, the major wheat QTL identified in Sumai 3 (Buerstmayr et al., 2009) and Wangshuibai (WSB; Jia et al., 2018), both bred in China, is often used for breeding wheat varieties more tolerant to FHB (Berraies et al., 2020; Ma et al., 2019; Rawat et al., 2016). *Fhb1* presents type II resistance to several species of *Fusarium,* and consistently exhibits moderately high resistance to FHB (Hao et al., 2020). Screening efforts in wild wheat relatives are also used to increase available sources of resistance, notably identifying a QTL from the wheatgrass *Thinopyrum elongatum*, *Fhb7*, encoding the trichothecene detoxification enzyme glutathione S-transferase, which detoxifies DON through de-epoxidation (Wang et al., 2020). In barley, QTLs associated with FHB resistance, DON accumulation, and kernel discoloration have also been identified (de la Pena et al., 1999; Huang et al., 2021; Ogrodowicz et al., 2020; Sallam et al., 2023). However, the coincident nature of the QTLs associated with FHB resistance and the agricultural traits inherent in these lines makes breeding efforts complicated in barley. To better elucidate the relationship between QTLs and agricultural traits, a moderately susceptible cultivar, Rasmusson, was crossed with PI383933, a highly susceptible, short-stature Japanese landrace with a dense spike. The recombinant inbred lines showed a correlation of FHB severity with the morphological traits, where the plant height and spike length were negatively correlated, and the spike density was positively correlated with disease severity (Huang et al., 2018).

Recently, the gene responsible for the Fhb1 resistance within the QTL has been identified in wheat. Su et al. (2019) and Li et al. (2019a) have identified a gene in the Fhb1 region in Sumai 3 and WSB, TaHRC, and

Qfhs.njau-3B, respectively, which encodes a histidine-rich calcium-binding protein (His). They found that a deletion mutation spanning the start codon in the His gene confers FHB resistance in wheat. Thus, the wild-type His gene functions as a susceptibility determinant regulating the FHB symptoms (Li et al., 2019a; Su et al., 2019). Experiments by Su et al. (2019) suggest that the mutated gene did not acquire a new function, but rather enhanced FHB resistance. The His gene has been shown to localize in the nucleus, suggesting its potential role in altering host immunity-related processes (Li et al., 2019a). The *T. elongatum* genome sequence was used to clone and characterize a gene *Fhb7* identified as having an origin in *Epichloe,* an endophyte of grasses (Wang et al., 2020). More recently, the homologs of *Fhb7* were reported in other genera of grass, including *Elymus*, *Leymus*, *Roegneria,* and *Pseudoroegneria* (Guo et al., 2022). In addition, Guo et al. (2023) found a contrasting reaction to FHB in wheat-*Thinopyrum* substitution and translocation lines, with some lines carrying glutathione S-transferase encoding *Fhb7* homolog showing FHB susceptibility. Wang et al. (2023) transformed a single strain of the endophytic fungus *Phomopsis liquidambaris* to produce Fhb1. When inoculated separately into wheat, which was then challenged by *F. graminearum*, spike disease was reduced by 25.7% and 24.7%, with significantly reduced DON levels in grain. Although more extensive work needs to be done before using this method commercially, the study indicates that engineered endophytes can reduce disease and, importantly, extends the possibilities of using endophytes for plant protection by expressing plant resistance genes.

Transgenic breeding provides new possibilities for developing FHB resistant cultivars, which has advantages over conventional breeding methods due to its ease of transferring candidate genes relevant to FHB resistance, especially with genome editing technologies like CRISPR/Cas9. Recently, overexpression of the non-specific lipid transfer protein (AtLTP4.4) from *Arabidopsis* into wheat demonstrated reduced DON accumulation (McLaughlin et al., 2021). In addition, UDP-glycosyl transferases (UGT) produced in plants such as *Arabidopsis* and barley have been identified as being involved in detoxifying DON (Poppenberger et al., 2003; Xing et al., 2017). The transgenic expression of UGT in wheat reduced DON accumulation and FHB severity by suppressing pathogen spread in the spike, contributing to type II resistance (Gatti et al., 2019; He et al., 2020; Li et al., 2015; Shin et al. 2012). Another study reported the successful reduction of FHB in barley via overexpression of an antifungal gene, nepenthesin 1 (Bekalu et al., 2020), thus identifying another transgenic opportunity for disease resistance against FHB. Multiple resistance genes can be used for stronger resistance through gene pyramiding (Joshi and Nayak, 2010). The engineering of constitutive expression of two barley genes, UGT, and a pectinase inhibitor (*AcPMEI* or *PvPGIP2*), into wheat contributed enhanced resistance to FHB (Mandalà et al., 2021). Similarly, the overexpression of multiple genes connected to FHB resistance may permit broad-spectrum resistance in crops. The induced expression of multiple defense response genes, including those encoding α-1-purothionin, thaumatin-like protein 1, and β-1,3-glucanase in wheat, significantly enhanced the FHB resistance (Mackintosh et al., 2007). Thus, several research groups have successfully generated wheat and barley lines with enhanced resistance to FHB through genetic engineering using these approaches. However, no wheat varieties are highly resistant at this time (Fabre et al., 2020), and with the barriers of introducing external genes into commercial varieties (Entine et al., 2021), it may be a long time until fully resistant transgenic varieties are available to growers.

2.4. Biological control of FHB and importance of the host microbiome

The role of the individual members of the host microbiome in protecting plants against pathogen infection is under intensive study, and the impact of the community structure is being revealed in hosts of *F. graminearum* (Kavamura et al., 2021; Solanki et al., 2021). Individual community members can thwart host-plant colonization by *Fusarium* pathogens through strategies, including antibiosis, niche competition, and host defense induction (Gdanetz and Trail, 2017; Gdanetz et al., 2021; Karlsson et al., 2021; Longley et al., 2020; Rojas et al., 2020). Numerous studies have demonstrated the ability of microorganisms to biotransform or biodegrade mycotoxins, and to increase yield (Gao et al., 2018; Hassan et al., 2021; Liu et al., 2022; Noel et al., 2022). Thus, the utilization of microorganisms is a promising means of controlling FHB and mycotoxins in plants (Fig. 2), where the microbes can be native, applied, or both.

Inhibitory interactions between the host and pathogen can be direct, most commonly, or indirect. In direct inhibition, microbes weaken the effect of the pathogen through mycoparasitism or production of bioactive chemicals. Mycoparasitism involves a microbe that parasitizes the fungus, for example, the effect of the biotrophic fungus *Sphaerodes mycoparasitica* and the necrotrophic *Trichoderma harzianum* on reducing colonization of the host plant by *F. graminearum* (He et al., 2019; Vujanovic and Goh, 2009). *S. mycoparasitica* is a biotroph originally isolated from Canadian fields in association with *F. avenaceum*, *F. graminearum,* and *F. oxysporum* (Kim and Vujanovic, 2016; Vujanovic and Goh, 2009). Both *in vitro* and *in planta* assays demonstrated the ability of *S. mycoparasitica* to penetrate the *F. graminearum* hyphae and hinder hyphal growth (Vujanovic and Goh, 2012, 2011). In addition to growth inhibition, *S. mycoparasitica* degrades mycotoxins produced by *F. graminearum* resulting in less toxic metabolites (Kim and Vujanovic, 2017; Kim and Vujanovic, 2022; Powell et al., 2023). Direct inhibition of the growth of pathogenic fungi has been documented through antagonistic compounds such as antifungal metabolites (Hao et al., 2021b). A recent study demonstrated inhibition of spore germination and mycelial growth in *F. graminearum* by the yeasts *Meyerozyma guilliermondii*, *Cyberlindnera saturnus*, *Rhodotorula glutinis*, and *Cryptococcus carnescens* (Podgórska-Kryszczuk et al., 2022). Studies of enzymatic antagonism demonstrated the attenuating impacts of hydrolytic enzymes, including chitinases, glucanases and proteases produced by microbes (Dominelli et al., 2022; Kim et al., 2019; Li et al., 2016b; Swiontek Brzezinska et al., 2014).

Indirect inhibition of fungal growth can be manifested by the host or through the effects of microbes colonizing the host or rhizosphere. Microbes can promote plant growth, resulting in the priming of plant defense responses, or stimulate the plant's overall health by releasing stimulatory volatiles, phytohormones or by improving the host nutrient acquisition capacity (Adnan et al., 2022; Ilyas and Bano, 2012; Jha, 2020; Qu et al., 2020; Vandana et al., 2021). Induced systemic resistance primes the plant immune system, leading to more efficient activation of immune responses, a common outcome of beneficial mycorrhizal-plant relationships (Ali et al., 2023; Constantin et al., 2019; Jung et al., 2012; Teixeira et al., 2019). Microbes can also affect each other through nutrient competition and/or niche exclusion, which can be facilitated by disease attenuated strains. In *F. graminearum,* deletion mutants of the *Tri6* and NADH oxidase genes, have reduced pathogenicity and activate FHB resistance in wheat (Ravensdale et al., 2014). Beneficial microbes residing in the host plant or the rhizosphere influence disease severity by interacting more efficiently with the host plant than the pathogens, causing competitive exclusion of the pathogens (Busby et al., 2016; Medina et al., 2017). Integrating multiple levels of management approaches affords both healthier crops and increased tolerance to disease pressure.

Plant-associated microbiomes play an important role in maintaining plant fitness by combating other microbial pathogens and insect herbivores. A recent study revealed the potential of bacterial members of the wheat head microbiome to reduce the virulence of *F. graminearum.* Among the bacterial isolates, *Pseudomonas piscium* modified fungal histones through the activity of phenazine-1-carboxamide, which consequently reduced fungal growth and virulence (Chen et al., 2018b). Microbial antagonists isolated from wheat anthers, including *Bacillus subtilis/amyloliquefaciens* and *Cryptococcus* spp., demonstrated a reduction in FHB disease symptoms and increased grain weight (Khan et al.,

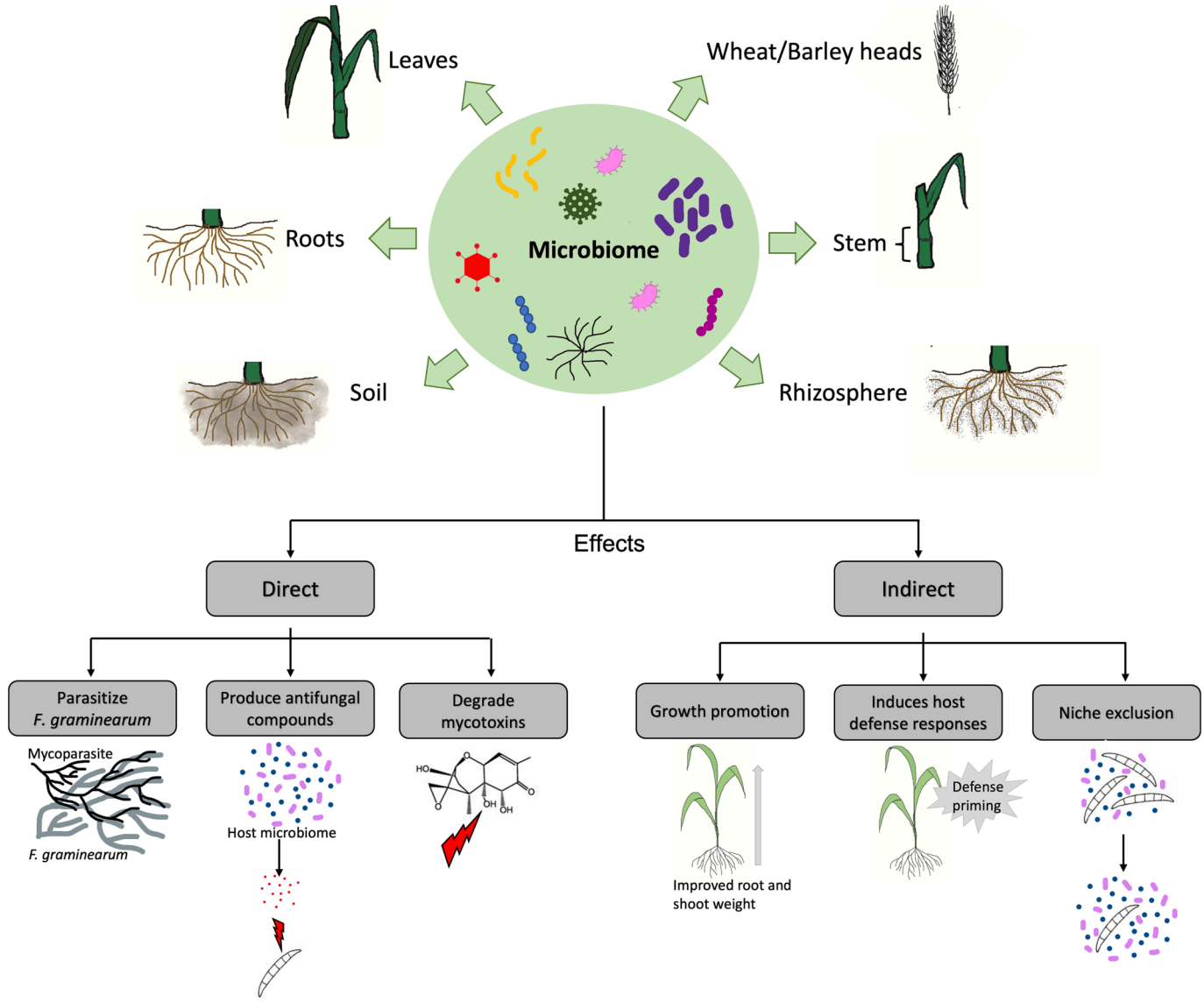

Fig. 2. Overview of microbiome mediated FHB management. Microbial members, colonizing host tissues or from the rhizosphere, can protect plants from *F. graminearum* directly or indirection through parasitism, niche competition, detoxifying mycotoxins, antifungal metabolite production, and by triggering host defense responses. The beneficial microbes of the host microbiome can also promote plant growth.

2001). An endophytic fungus, *Simplicillium lamellicola*, isolated from the roots of the wheat cultivar AC Morely was found effective in reducing *F. graminearum* infections on wheat in field conditions. Moreover, *S. lamellicola* displayed plant growth promoting properties by increasing shoot and root length as well as fresh and dry weight of wheat cultivars (Abaya et al., 2021). Besides antagonistic effects, microbial candidates that can degrade, adsorb, or transform the fungal mycotoxins have been characterized. DON was converted into 3-epi-DON and 3-keto-DON by various bacteria found both in soil and wheat tissue (Völkl et al., 2004). In contrast to DON, 3-epi-DON and 3-keto-DON form weaker bonds with the ribosome, the mode of action for DON toxicity, leading to less stable binding, and do not induce ribotoxic stress response in the plant (Payros et al., 2016). Degradation of DON and formation of derivatives have been seen in species of the bacterial genera *Nocardioides* and *Devosia*, which are residents of the wheat phyllosphere and rhizosphere (Ikunaga et al., 2011; Wachowska et al., 2017; Zhang et al., 2021). The application of DON degrading microbial candidates from the host phyllosphere or rhizosphere microbiome is a promising approach for FHB management.

Viruses remain one of the most understudied facets of the plant microbiome, but our understanding of them has greatly increased recently because of the advancement and widespread use of sequencing techniques that better capture their genetic information. Mycoviruses are those that specifically infect fungi, and as of 2019, there were 29 fully sequenced mycoviruses identified from members of the genus *Fusarium* (Li et al., 2019b). In most cases, mycovirus infection causes little or no symptoms in the fungal host (Son et al., 2015). However, some mycoviruses can cause phenotypic alterations to virus disease cycles, reducing (hypo-) or increasing (hyper-) virulence on the host (Li et al., 2019b; Nuss, 2005; Pearson et al., 2009; Sharma et al., 2018). Hypo-virulent viruses have promising bio-control mechanisms, as they have been shown to reduce mycelial growth, decrease virulence in wheat, and demonstrated substantial reduction in trichothecene production (Son et al., 2015). Mycoviruses from the family *Fusariviridae* and *Crysoviridae* are associated with hypovirulence in *F. graminearum* (Chu et al., 2002; Darissa et al., 2012).

Numerous studies highlight the importance of bacterial, fungal, and viral candidates as potential biocontrol agents against *F. graminearum*. Although the application method of these biocontrol agents depends on multiple factors such as weather conditions, crop stage, formulation,

and the type of agent, the most widely used methods include seed treatment, spraying, and soil drenching (Elnahal et al., 2022). The application of bacterial biocontrol inoculum via seed coating (Mattei et al., 2022) or spraying on heads (Baffoni et al., 2015) has shown effective biocontrol against FHB in wheat. The off-target impacts of fungicides on native or applied microbial agents should be studied more in-depth, and in the context of *F. graminearum* infection. Such studies should seek the most effective use of fungicides, while minimizing losses to ecosystem function due to off target impacts. In addition to optimizing the use of microbial agents to control FHB, it is essential to understand how *F. graminearum* employs its effector proteins to modulate the microbiome composition and promote disease development in the host.

2.5. Effector proteins and application in management strategies

Insight into the molecular pathways employed by *F. graminearum* to initiate colonization in host plants is essential for the development of novel control strategies. Fungal effectors are proteinaceous or non-proteinaceous secreted molecules that serve to modulate the host's defense responses, ultimately promoting successful colonization by the fungus on the host (Pradhan et al., 2021; Rocafort et al., 2020; Wilson and McDowell, 2022). Increasing evidence shows that proteins that are larger in size and lower in cysteine content can also function as effectors (Sperschneider et al., 2015; See et al., 2019). The functions of effectors are not limited to virulence contributions, but are also involved in triggering plant cell death (Yang et al., 2021a), nutrient-acquisition, and competition with other microbes (Bradley et al., 2022). Because effectors are so important to disease, and also an evolving field of research, we briefly summarize the progress on research in this area, and comment on the possible efficacy of management strategies that work against effectors.

The advancement of omics tools allows the use of *in silico* approaches to identify proteins with putative effector functions in *F. graminearum* (Alouane et al., 2021; Brown et al., 2012; Fabre et al., 2019; Hao et al., 2021c; Tu et al., 2023; Yang et al., 2021a). Transcriptional datasets document expression patterns of candidate effectors, suggesting their involvement in fungal-host interactions (Chen et al., 2021b; Mentges et al., 2020; Rocher et al., 2022). Prediction tools identify candidate effectors, leaving the experimental validation of their role in pathogenesis. FgNls1 is an effector protein in *F. graminearum* with a eukaryotic nuclear localization signal, which interacts with the wheat histone 2B protein. Transgenic wheat plants that silence FgNls1expression suppressed FHB symptoms (Hao et al., 2023). Recently, Fg12, a secreted ribonuclease effector, has been characterized and shown to contribute to fungal virulence and cell death in the host (Yang et al., 2021a).

Specialized metabolites such as DON can act as non-proteinaceous effectors (Collemare et al., 2019), and they can influence the microenvironment by altering the pH, nutrient availability, or other factors, creating conditions conducive to microbial growth. Numerous specialized metabolites produced by the *Fusarium* spp. have antimicrobial effects (Mentges et al., 2020; Xu et al., 2023); therefore, besides virulence promotion, specialized metabolites acting as effectors can help the producing microbe to compete with other microbes colonizing the host (Snelders et al., 2020). An increasing number of transcriptomic studies report the involvement of multiple specialized metabolites during different stages of *F. graminearum* colonization on the host (Mentges et al., 2020, Miguel-Rojas et al., 2023). For instance, Jia et al. (2019) demonstrated that fusaoctaxin A facilitates cell-to-cell penetration by the fungus during infection and suggests a role in manipulating host nutrient transport. Similarly, a wide array of hydrolytic enzymes produced by *F. graminearum*, such as cell wall degrading enzymes have been described as effectors (Bradley et al., 2022; Garcia-Ceron et al., 2021), and are involved in plant cell wall penetration and necrosis of host tissues (Hao et al., 2021c; Zhao et al., 2014). A recent study demonstrated that the knockdown of the plant cell wall degrading enzyme xylanase A remarkably reduced fungal virulence toward wheat and barley, suggesting its role in the infection process and disease development (Tini et al., 2020). The accumulating evidence indicates effectors are the key determinants of fungal pathogenicity, however, the identification of putative effectors through bioinformatics tools has limitations, as these tools predict protein function based on predetermined properties (e.g. numbers of amino acids, cysteine residues, or secretion signals) that may exclude the candidates without well-characterized effector properties (Alouane et al., 2021). Recently, Miltenburg et al. (2022) used proximity dependent biotin identification, a new method that permits the study of protein interactions *in vivo* to identify candidate effector proteins in the *F. graminearum* - *Arabidopsis* pathosystem. With new methods emerging for discovering effectors, we may identify effector molecules that can be targeted in control of plant diseases. Additionally, the characterization of the effector targets in the host can be used as a guide to identify the disease susceptibility genes in the host (Gawehns et al., 2013).

2.6. Molecular tools for control: RNA induced gene silencing of *F. graminearum*

RNA-induced gene silencing (RNAi) is a transcriptional or post-transcriptional level mechanism used by many organisms to knock down (or silence) the expression of target genes via homology-dependent mRNA degradation. RNAi has emerged as a promising tool for manipulating gene expression in a multitude of organisms including plants, animals, and fungi. The process is triggered when a long double-stranded RNA (dsRNA) is cut or "diced" into small fragments ~ 21 bp long by a ribonuclease III enzyme called Dicer (Gaffar et al., 2019; Hannon, 2002; Hao et al., 2021a; Lee et al., 2010). These small fragments, known as siRNAs (small interfering RNAs), subsequently bind to a family of proteins known as argonaute. Together, the argonaute proteins and the siRNAs form the RNA-induced silencing complex (RISC). The activation of the RISC complex occurs when one of the two strands of siRNA is removed, allowing the remaining strand to bind to the complementary mRNA. Once bound, the argonaute proteins will cleave the mRNA, thus degrading it and accomplishing the knockdown of the gene (Dang et al., 2011; Gaffar et al., 2019; Koch et al., 2013). In *F. graminearum*, the silencing components include two dicer proteins (FgDicer1 and FgDicer2), two argonaute proteins (FgAgo1 and FgAgo2), and five RNA-dependent RNA polymerases (FgRdRp1-5) (Chen et al., 2015). Several studies have demonstrated RNAi as an effective strategy to enhance disease resistance in plants against phytopathogens including *Fusarium* spp. (Gu et al., 2019; Machado et al., 2018; Tetorya and Rajam, 2021), *Aspergillus flavus* (Arias et al., 2015; Gilbert et al., 2018), *Sclerotinia sclerotiorum*, *Botrytis cinerea* (McLoughlin et al., 2018, Sabbadini et al., 2021), *Blumeria graminis* (Hein et al., 2005; Nowara et al., 2010), *Cochliobolus sativus*, *Colletotrichum truncatum*, *Magnaporthe oryzae* (Gu et al., 2019), and *Colletotrichum gloeosporioides* (Mahto et al., 2020). RNAi is advantageous to use because it is a non-chemical process and can be developed to target specific genes and pathogens, which may reduce the ability for resistance to develop, as well as limit off-target effects.

There are two common methods for introducing the target RNAi construct into cells to begin this process: host-induced gene silencing (HIGS) and spray-induced gene silencing (SIGS) (Hao et al., 2021). In HIGS, the host machinery is used to silence pathogen genes. This is often accomplished by using transgenics to insert pathogen genes into the plant host genome. Genes that form a hairpin structure will easily trigger the gene silencing machinery (Cheng et al., 2015; Koch et al., 2013). The introduced genes are specific to the target pathogen(s) and reflect proteins the host plants would commonly encounter during initial infection, such as effector proteins (Koch et al., 2013). Thus, when a pathogen infects, the plant has the machinery to thwart the expression of genes essential for disease production by the pathogen. In a study published by Koch et al. (2016), the successful knockdown of the *CYP51* gene in *F. graminearum*, essential to ergosterol biosynthesis, was accomplished

by applying the HIGS method in barley. The knockdown of certain host genes may also promote disease resistance to FHB. For instance, in wheat, the RNAi mediated knockdown of *TaT1R1*, the gene encoding the auxin receptor, was shown to contribute to FHB resistance (Su et al., 2021). The involvement of auxin signaling in promoting susceptibility to FHB infection has been previously demonstrated (Brauer et al., 2019), and the silencing of the auxin receptor gene in the host via RNAi inhibited the hyphal extension of *F. graminearum* in the rachis (Su et al., 2021). HIGS has successfully been used in trials of wheat and barley to combat multiple pathogens, including *F. graminearum*, *Puccinia triticina*, and wheat mosaic streak virus (Cheng et al., 2015; Koch et al., 2013). HIGS is transgenically-generated, and its use in the field needs to overcome regulatory barriers and public concerns.

RNAi can also be initiated through SIGS, which employs the exogenous application of the dsRNA or siRNA product on the surface of crops, similar to pesticide applications, and is taken up by the pathogen during initial plant infection or by the plant during growth. In the first scenario, the fungus takes up dsRNA or siRNA from the plant surface, and is processed by fungal RNAi machinery. In the latter instance, plants take up the RNAi structures and process them into functional siRNA using plant RNAi machinery. The siRNA molecules are then translocated into fungal cells via exosomes, passive diffusion, or membrane associated receptors (Machado et al., 2018; Wang and Jin, 2017). This approach avoids the regulatory issues with HIGS, and cellular mechanisms from either the host or the pathogen can be targeted. Additionally, there is evidence that host plants will amplify the silencing signal throughout the plant beyond the initial point, making it a systemic control mechanism (Cai et al., 2018a). The spray application of the same dsRNA targeting the *CYP51* genes inhibited fungal growth on locally sprayed parts of detached barley leaves and distal (non-sprayed) regions (Koch et al., 2016). SIGS of RNAi constructs targeting genes in *F. graminearum* encoding chitin synthase 7, glucan synthase, and protein kinase C displayed silencing effects and significantly reduced the fungal infection on wheat spikelets under greenhouse conditions (Yang et al., 2021b). Although SIGS has benefits over HIGS, one major concern is the short-term instability of RNAi structures before being taken up by the host plant or pathogen (Machado et al., 2018). The limitations in achieving stability of SIGS based RNAi constructs for FHB disease management points to future work, which should determine whether or not combinations of SIGS and fungicides are possible.

3. Perspectives

FHB has caused large yield losses throughout the last 100 years. In the 1990′s, studies demonstrated that tillage provides some control of *F. graminearum* emergence in the spring and, together with crop rotation using non-susceptible crops, can be highly effective (Miller et al., 1998; Dill-Macky and Jones, 2000). These management measures have limitations that impact their efficacy in controlling this devastating disease and the sustainability of production. Thus, there is a growing need for innovative approaches to managing FHB. The future of FHB management lies in multidisciplinary approaches that incorporate advances in genomics, genetic-engineering, new fungicide chemistries, applied biocontrol, and consideration of the life cycles of FHB causing *Fusarium spp*.

Use of genomics and transcriptomics has significantly advanced identification and characterization of genes involved in virulence and infection processes on the pathogen side, and resistance on the host side. Engineering FHB resistance traits in plants through genome editing promises efficient and sustainable approaches to managing FHB. The RNAi based approach also holds a key position in the future for FHB management. Recently, nanoparticles have been used to deliver DNA and RNA to plants and animals for transformation and for medical applications (Sharma and Lew, 2022; Zhang et al., 2019; Zhi et al., 2022). Silicon, which can package the particles for delivery, is known to protect from UV radiation (Chen et al., 2016; Tripathi et al., 2017). These two developments should allow more effective uses of SIGS and HIGS in large-scale agricultural applications. Development of alternative methods such as CRISPR-Cas9 and future techniques for genomic modification may, in the long run, provide a low risk that is acceptable to a worldwide community.

Fungicides play an integral role in FHB management, however, the emergence of fungicide resistance to multiple classes of fungicides, demonstrating the highly adaptive nature of the fungus. Moreover, the escalating use of fungicides on crops has an impact on the environment, human and animal health. Fungal effectors have specific functions and structures that can be used to design inhibitors that selectively block effector activity. These inhibitors can be developed into fungicides that specifically target *F. graminearum* without harming beneficial organisms. Furthermore, numerous studies have shown the potential of novel antifungal chemistries from plants, other fungi, and lichens in controlling FHB. Technologies such as remote sensing help to monitor the status of the plant health and detect early signs of FHB (Xiao et al., 2022; Zhang et al., 2022). Remote sensing allows the targeted and timely application of fungicides, thereby minimizing prolonged and intense fungicide use, which may slow down the emergence of fungicide-resistant strains.

The intimate interactions of host-associated beneficial microbes in defending against pathogen attack holds huge promise in managing FHB. Although the ability to manipulate the host microbiome is in its infancy, there is data indicating the role of beneficial players from the host microbiome in controlling phytopathogens, including mycotoxin reduction and enhanced yield. The difficult challenge ahead is to understand the complex relationships among beneficial microbes, hosts, and pathogens, and the need to develop an appropriate intervention strategy.

Although *F. graminearum* produces secondary inoculum in the form of conidia, it behaves epidemiologically as a monocyclic disease (Sutton 1982), with ascospores providing the primary inoculum. This aspect of the life cycle, combined with the fact that tillage is a very effective control, suggests that addressing the formation and dispersal of ascospores would be a highly effective target for novel controls of this disease. In recent years, our understanding of the interactions of *F. graminearum* with host plants, resulting in perithecium development, has greatly improved (Chen et al., 2023; Imboden et al., 2018; Prussin et al., 2014; Schmale et al., 2005; Shin et al., 2020; Sikhakolli et al., 2012; Trail et al., 2017). Management of primary inoculum thus appears to offer promising outcomes for control. This might be achieved through identifying means of rapid deterioration of crop residues after harvest, particularly in wheat and maize. In wheat, perithecium initials are present at harvest in the stalks and heads, and initiate perithecia after being primed by cold and dry weather (Guenther and Trail, 2005). There are some indications that rain in the fall will stimulate conidial production, using up stored lipid reserves that fuel perithecium development in the spring (Guenther et al., 2009; Trail and Common, 2000). Maize stalks support longer term inoculum production. Biological control measures that treat colonized stalks would be eco-friendly proactive approaches to reducing perithecium maturation. Recently, Xu et al. (2022) characterized the antagonistic properties of bacterial isolates from the microbiome of *F. graminearum* perithecia collected from wheat fields. Isolates of *Pantoea agglomerans* inhibited mycelial growth, perithecium formation, and mycotoxin biosynthesis. Additional studies targeting the crop residues for limiting inoculum would likely have beneficial outcomes.

After nearly 35 years of continuous research support by the USDA Wheat and Barley Scab Initiative, and funding worldwide to study this disease, two recent discoveries about *Fusarium* have provided what are likely major new targets for control. Extracellular vesicles (EVs) have been shown to be part of host-pathogen interactions in a number of mammalian and plant diseases, and are known to provide cross-kingdom communication through transmitted proteins, nucleic acids and specialized metabolites, including virulence factors (Bleackley et al., 2020; Cai et al., 2018b; Garcia-Ceron et al., 2023, 2021; Mathieu et al.,

2019; Motaung and Steenkamp, 2021; Rodrigues et al., 2008; Rybak and Robatzek, 2019; Wang et al., 2015b). In addition, *F. graminearum* was shown to produce biofilms (Shay et al., 2022), which are likely to play an active role in pathogenicity, particularly disease initiation. Although the roles for EVs and biofilms in *Fusarium* spp. and their role in disease are yet to be fully elucidated, they are likely to provide new targets for scientific ingenuity in head blight control.

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 paper.

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