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Understanding the mechanisms underlying biological control of *Fusarium* diseases in cereals

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Abstract Many *Fusarium* species cause serious diseases for cereal cultivation. These include Fusarium head blight and crown rot on wheat and bakanae disease on rice. These represent a major concern both in terms of food security and food safety. The latter is connected with the risk of mycotoxin contamination of grains. Biological control has proven its potential for controlling head blight and crown rot diseases of cereals caused by *Fusarium* species in a number of studies, and indeed several commercial products are under development. We review current knowledge of the mechanisms underlying biological control with a focus on fungal biocontrol agents, and also include challenges related to co-occurrence of *Fusarium* species. Several of the established biological control mechanisms (antibiosis, competition, hyperparasitism and induced resistance) can act simultaneously, thus resulting in disease control and, consequently, reduction of mycotoxin contamination. We also review the biological roles of some of the many mycotoxins produced by *Fusarium* species, and the mechanisms by which they are detoxified by cereal enzymes or by other fungi and how biological control agents (BCAs) can stimulate their degradation. Finally, the effect of biocontrol agents on the resident microbiota, as well as the effect of the resident microbiota on the performances of BCAs, are discussed. New perspectives on the use of biocontrol agents for the management of Fusarium diseases on cereals.

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Introduction

The fungal genus *Fusarium* includes organisms able to cause disease or otherwise affect a wide range of hosts from mammals to plants. Among plants, cereals are important hosts for especially pathogenic *Fusarium* species worldwide. These pathogens cause two diseases in cereals: crown (foot) rot causing losses in seedlings and more importantly head blight causing contamination of grain with mycotoxins. Biological control, using both beneficial bacteria and fungi, has been developed and even commercialised especially for head blight (Collinge et al., 2022). This review focusses on our understanding of the primary roles of mycotoxins and an evaluation of the mechanisms employed by different biological control agents (BCAs).

The diseases

A range of *Fusarium* species (roughly 30, see table 1) can cause both head blight disease (FHB) and root and crown rots of cereals (Rojas et al., 2019, Nielsen et al., 2011, Tan et al., 2020, Munkvold et al., 2021) as well as kernel rot of maize (Gong et al., 2015b) and rice (Matic *et al.*, 2017). *Fusarium* diseases affect

Table 1 *Fusarium* species affecting cereals

Species	Disease	Reference
F. graminearum	FHB, FCR, GER	Bowden & Leslie, 1999; Yerkovich *et al.*, 2020; Dinolfo *et al.*, 2022
F. culmorum	FHB, FCR, GER	Rojas *et al.*, 2019; Dinolfo *et al.*, 2022
F. poae	FHB, FCR	Rojas *et al.*, 2019
F. pseudograminearum	FHB, FCR	Rojas *et al.*, 2019
F. avenaceum	FHB, FCR, GER	Rojas *et al.*, 2019; Dinolfo *et al.*, 2022
F. sporotrichioides	FHB	Rojas *et al.*, 2019
F. langsethiae	FHB	Rojas *et al.*, 2019
F. asiaticum	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. meridionale	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. ussurianum	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. boothii	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. nepalense	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. mesoamericanum	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. vorosii	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. *louisianense*	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. aethiopicum	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. brasilicum	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. gerlachii	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. acaciae-mearnsii,	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. cortaderiae	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. austroamericanum	FHB	Aoki *et al.*, 2012; Chen *et al.*, 2022
F. fujikuroi	Bakanae disease	Ou, 1985; Matic et al., 2017; Matic et al., 2017
F. verticillioides	Bakanae disease; FER	Ou, 1985; Matic et al., 2017; Logrieco *et al.*, 2002; Matic et al., 2017; Logrieco *et al.*, 2002
F. proliferatum	Bakanae disease; FER	Ou, 1985; Matic et al., 2017; Logrieco *et al.*, 2002; Matic et al., 2017; Logrieco *et al.*, 2002
F. subgutinans	Fusarium ear rot	Logrieco *et al.*, 2002
F. crockwellense	GER	Dinolfo *et al.*, 2022

FHB Fusarium head blight, *FCR* Fusarium crown (foot) rot, *FER* Fusarium ear rot, *GER* Gibberella ear rot small grain cereals such as wheat, both durum (*Triticum turgidum* subsp. *durum*) and bread wheat (*T. aestivum*), as well as oat, barley and triticale (*Avena sativa*, *Hordeum vulgare*, x *Triticosecale*) and maize (*Zea mays*).

Fusarium graminearum is considered as one of the most virulent casual agents of Fusarium head blight (FHB), also known as Fusarium scab (Fig. 1). In addition to *F. graminearum* (Bowden & Leslie, 1999, Yerkovich et al., 2020), other species included within the *Fusarium graminearum* species complex (Chen et al., 2022) have been shown to concur to FHB mostly in cool regions. In addition, some of these species are also associated with Fusarium crown rot (see Table 1). FHB and Fusarium crown rot are cosmopolitan diseases and have been reported in almost all areas where wheat and other cereals are cultivated. The predominance of one pathogenic species over the others is connected to the geographic localisation and environmental conditions. For example, *F. graminearum* is predominant in humid and cooler regions while *F. pseudograminearum* is found to be the main causal agent in arid and semi-arid regions (Akinsanmi et al., 2004, Xu & Nicholson, 2009). With respect to geographical distribution, a predominance of *F. graminearum* in Central and South East Europe has been described, followed by *F. culmorum*, *F. avenacenum* and *F. poae* (Bottalico & Perrone, 2002). The latter is considered a less pathogenic species (Xu et al., 2007b, Xu et al., 2007a). In Europe, a shift was shown in the predominance of these pathogens from *F. culmorum* to *F. graminearum* (Valverde-Bogantes et al., 2020), whereas the opposite has occurred in Canada since 2002, where *F. culmorum* increased compared to *F. graminearum* (Miller, 2002, Scherm et al., 2013). In China, there are three main causal agents of FHB; the presence of specific species may depend on climate conditions, with *F. asiaticum* predominant in the southern regions where average temperatures are above 15°C, whereas *F. graminearum* is more frequently reported in northern cooler regions (O'Donnell et al., 2004, Qu et al., 2008, Hao et al., 2017) and *F. culmorum* is often indicated as the dominant species in Western China. In Australia, FHB is regionally limited, where it is associated with *F. graminearum*, while *F. pseudograminearum* is considered an important threat as the main causal agent of Fusarium crown rot (Akinsanmi et al., 2004).

However, the scenario is actually much more complex, as detailed in a Danish study where wheat, barley, oat, triticale and rye seeds sampled from 2003 to 2007 and wheat and barley seeds sampled

Fig. 1 Symptoms of Fusarium head blight (FHB) on spikes © David B. Collinge, Sabrina Sarrocco and Giovanni Vannacci

from 1957 to 2000. These samples were analysed to determine the abundance of *Fusarium* spp. and the relative amount of mycotoxins. Among the interesting insights reported was that *Fusarium* spp. varies according to host, which is in line with the FHB ecology and distribution, while, on the other hand, very low or no *F. graminearum* was detected in older samples from 1957 to 2000 but was dominant in the wheat samples from 2003 to 2007 (Nielsen et al., 2011).

From an ecological point of view, due to the high variability of *Fusarium* species that can cause FHB or crown (foot) rot, it is generally accepted that competitive rather than synergistic interactions occur during the infection process of the host. In addition to environmental conditions, *Fusarium* species are specialised in their ability to produce specific specialised metabolites (also called secondary metabolites), namely mycotoxins that can play important roles, not only during the infection process, but, mainly in the inter-specific competition for host infection (Xu and Nicholson, 2009). The release of mycotoxins is a well-known phenomenon described for *Fusarium* species infecting cereals, where competition between species depends basically on temperature and host type (Simpson et al., 2000).

Among the Fusarium diseases occurring on cereals, recent studies on rice show that the *Fusarium fujikuroi* species complex, mainly represented by three species (Table 1), *i.e.*, *F. fujikuroi* (syn. *F. verticillioides*) and *F. proliferatum*, is recognised as being responsible for bakanae disease (Ou, 1985; Matic et al., 2017). Bakanae disease can cause crop losses reaching up to 70% in rice-producing states of India (Bashyal et al., 2022), thereby emerging as a major risk to food security in those regions (Bashyal, 2018). The typical symptoms of this disease are slender, chlorotic and elongated primary leaves as a consequence of the production of the phytohormone gibberellin by the pathogen. These symptoms led to the Japanese name bakanae, meaning ‘foolish seedling’ (Amatulli et al., 2010). In addition, infected seedlings can show different symptoms, such as crown rot, thus resulting in stunted plants (Wulff et al., 2010).

In maize, the *Fusarium fujikuroi* species complex is also recognised as the main causal agent of Fusarium ear rot (or pink ear rot or pink fusariosis) and red ear rot (syn. of *Gibberella* ear rot) (Table 1). With respect to pink ear rot, the occurrence of *Fusarium* species depends primarily on environmental conditions; in Europe, *F. verticillioides* and *F. proliferatum* predominate in drier and warmer regions like Italy and Spain, while, under colder and more humid conditions, *F. subglutinans* is usually isolated more frequently than *F. proliferatum* and *F. verticillioides* (Logrieco et al., 2002; Goertz et al., 2010). Species such as *F. graminearum* (predominate in years and regions with frequent rainfall and moderate temperatures) and *F. culmorum*, *F. croockwellense* and *F. avenaceum* (more common in central and northern Europe) are indicated as causal agents of red ear rot (Reid et al., 1999, Dinolfo et al., 2022).

Fusarium mycotoxins

The majority of *Fusarium* species that attack cereals are feared as much as a source of mycotoxins that contaminate the grain before harvest (Bryła et al., 2018, Antonissen et al., 2014) as for direct yield loss (Savary et al., 2019). Neither disease resistance nor chemical control are effective measures for efficient disease control in wheat (Rojas et al., 2019), barley (Janssen et al., 2018) or oats (Gorash et al., 2017), and thereby eliminate the risk of mycotoxin contamination of grains. Biological control and transgenic disease resistance each offer some promise as alternative and sustainable strategies for control of these diseases. We will look into the biology of the interactions of these fungi with their hosts and the mechanisms underlying these technologies to discuss their potential. Mycotoxins are defined as specialised (secondary) metabolites produced by fungi infesting our food that are toxic to vertebrate animals, in practise humans or our livestock (Agriopoulou et al., 2020). The physiological effect on mammals differ and encompasses induced organ necroses, carcinogenicity, immunosuppressive effects and mode of action include oxidative stress, inhibition of protein biosynthesis and emulating hormones (Pierzgalski et al., 2021). Several chemically distinct classes of mycotoxin have been described from *Fusarium* species (exemplified in Fig. 1), and there are many variants of some of these (Bottalico & Perrone, 2002, Desjardins, 2006, Nielsen et al., 2011), e.g. dozens of trichothecenes have been described from *Fusarium* species and some other genera in the order Hypocreales

(McCormick et al., 2011, Ji et al., 2019, Khodaei et al., 2021).

Biological roles of mycotoxins

We focus on mycotoxins for the anthropomorphic reason that they are toxic to us and our livestock. However, the fungi produce them for other reasons, not all clear, but the essence is that they give the producer a competitive advantage in their natural habitat. In this review we focus on *Fusarium* spp. In relation to their functions as plant pathogens, they can also compete as saprophytes in the absence of a living host, for example on crop debris (Rojas et al., 2019, Adam et al., 2015, Venkatesh & Keller, 2019, Sarrocco et al., 2021).

Soil is the main habitat of most of the cereal *Fusarium* species. Here these fungi can engage intimate interactions with other organisms, where mycotoxins offer protection from competing microbes (Venkatesh & Keller, 2019). For example, *F. fujikuroi*, one of the causal agent of foolish seedling disease, can respond to the presence of *Ralstonia solacearum* (wilt-causing phytobacterium) by producing bikaverin and beauvericin, two mycotoxins with antibacterial activity (Spraker et al., 2018). Fusaric acid, produced by several *Fusarium* species, has been reported to be produced by *F. fujikuroi* as a mechanism of defence against *Pseudomonas protegens* with the aim to reduce its antibiotic activity (Quecine et al., 2016).

Some trichothecenes, *e.g.*, deoxynivalenol (DON) are demonstrated to be an important pathogenicity factor both in head blight and root rot infection processes. Thus, mutants in the *Tri*5 gene in *Fusarium graminearum*, which encodes a key enzyme of mycotoxin biosynthesis, trichodiene synthase, are impaired in their ability to cause FHB disease in wheat (Bai et al., 2002, Cuzick et al., 2008), but not on maize (Proctor et al., 1995). The same mutation affects infection of wheat roots by *F. graminearum* and *F. culmorum* (Winter et al., 2019), but interestingly not in *Brachypodium distachyon* roots (Ding et al., 2022). Gene silencing and over-expression of the trichothecene regulatory gene *Tri6* in *F. culmorum* resulted in strains exhibiting reduced or enhanced crown rot disease in wheat, respectively.

Strains belonging to the *F. fujikuroi* species complex are able to produce several mycotoxins and other bioactive specialised metabolites harmful for human and animal health (Desjardins et al., 2000). *F. fujikuroi* and *F. proliferatum* among others produce fumonisins. Deletion of *FUM*1, *FUM*6, *FUM*8 or *FUM*21 genes greatly reduced fumonisin production in *F. proliferatum* (Sun et al., 2019) and infection of rice spikes. Strains of *F. fujikuroi* adapted to banana lack the fumonisin gene cluster and cannot infect maize (Glenn et al., 2008). The expression of the *Fum* genes conferring fumonisin biosynthesis to this strain resulted in the ability to infect maize. It can therefore be inferred that fumonisins are a pathogenicity factor necessary for the infection of maize. Fumonisin B1 is an inducer of programmed cell death (PCD) in e.g., maize and *Arabidopsis*, and the judicious use of mutations affecting the signalling pathway in *Arabidopsis* suggests that fumonisin B1 helps the fungus hijack to the jasmonate pathway to cause PCD in its host (Zhang et al., 2015).

Zearalenone (ZEA) is produced by several *Fusarium* species including *F. graminearum* (Desjardins, 2006, Nahle et al., 2021). Their mode of action includes emulating the mammalian hormone oestrogen (Kuiper-Goodman et al., 1987) and the inhibition of the chaperone heat shock protein 90 (Torres Acosta et al., 2019). *Fusarium graminearum* strains mutated in the zearalenone biosynthetic gene *PKS4* (polyketide synthesis) were unaffected in their ability to infect barley roots (Lysøe et al., 2006). Both plants and BCAs can readily detoxify ZEA, *e.g.*, by glycosylation, and this may explain why it has not been demonstrated to have a direct role in pathogenicity in plant infection. We elaborate on this below.

Detoxification of mycotoxins

Plants have numerous glycosyltransferases (Bowles et al., 2005). UDP-glucuronosyl-transferases (UGTs) that conjugate DON or NIV with glucose to produce DON-3-Glc or NIV-3-Glc, makes plants more resistant to FHB and also crown rot. This has been demonstrated in several grasses, including cereals (*Brachypodium* (Gatti et al., 2018, Michlmayr et al., 2018, Michlmayr et al., 2015, Pasquet et al., 2016), wheat, barley (Michlmayr et al., 2018, Li et al., 2017), rice

(Michlmayr et al., 2018), oat (Khairullina et al., 2022)), The glycosylated forms are known as "masked mycotoxins" for two reasons. They are not routinely detected in monitoring since they have different chemical properties and secondly because it is likely that at least a proportion of the glycosylated toxins will be deglycosylated following consumption by animals. Indeed, the European Food safety agency, EFSA, has addressed these concerns. This "masking" thus differs from other types of detoxification where the mycotoxin is chemically degraded. The biocontrol agent *Clonostachys rosea* was shown to enhance conversion of DON into DON-3-Glc. Also the two DON-detoxifying UGTs were induced to much higher level in the presence of *C. rosea* (Khairullina et al., 2023). The type A T2-HT2 glucoside has been found as a detoxification product in barley (Meng-Reiterer et al., 2015) and oats (Meng-Reiterer et al., 2016). A second form of inactivation of trichothecenes by conjugation has been described in cereals, and the products are thought to be more stable. Thus S-glutathione conjugates of DON have been found in naturally infected wheat (Uhlig et al., 2016). Similarly, lager yeast *Saccharomyces pastorianus* both glycosylates and sulphonates the *Fusarium* trichothecene mycotoxins DON, T2, HT-2 (Nathanail et al., 2015).

Glucosylation is also described as a plant response to ZEA treatment (Michlmayr et al., 2017). The glucosylated form no longer inhibits the ATPase activity of HSP90 from wheat and *Arabidopsis* (Walther-Larsen et al., 1993; Torres Acosta et al., 2019). HSP90 is a common target for effector proteins produced by pathogens and is important in (effector-triggered immunity) ETI (Mukhi et al., 2020, Pennington et al., 2016). *Clonostachys rosea* can also detoxify ZEA by a different mechanism, namely by using the ZHD101 lactone hydrolase that breaks down ZEA (Kosawang et al., 2014b). Disruption of the *C. rosea* zdh101 gene reduced the ability of *C. rosea* to control *F. graminearum*. (Kosawang et al., 2014a).

Transcriptomic studies in *C. rosea* demonstrated that ZEA and DON induce both direct and indirect detoxifying efflux functions, *e.g.*, ABC-transporters (Kosawang et al., 2014a, Dubey et al., 2014). Transcriptomic studies also showed up-regulation of MFS transporters in *C. rosea* in presence of *F. graminearum* and may contribute to detoxification through efflux functions (Dubey et al., 2014).

A brief introduction to biological control solutions

A major challenge for agriculture world-wide is to provide sufficient safe food for the global population, whilst considering the challenge of preserving biodiversity as well as to exploit disease management strategies respectful for the environment. The management of plant diseases using commercial (BCAs) appears to be very promising (Collinge *et al*., 2022). However, biological control in the field has been plagued by the issues of unreliability in field environments and lower efficacy compared to disease resistance and chemical control using fungicides. Innovative research efforts have intensified since the 1970s, so biological contro has improved in efficiency and made the leap in quality to the point to be considered, currently, one of the driving forces for academic and industrial activities focused on sustainable agriculture and crop production.

Starting from 1974, (Baker and Cook, 1974), work on biological control has dichotomised, with one direction towards the transfer from the lab to the market of the research efforts dedicated to *Trichoderma* spp., and others paving the way to the study of the biological, genetically and evolutionary features underpinning the beneficial effects that one of the best-known BCAs *Trichoderma* spp. can exert in terms of disease control (Sarrocco, 2023).

BCAs can be defined as organisms such as bacteria, filamentous fungi and yeasts, as well as mycoviruses, which can be exploited for their ability to control plant pathogens, to reduce their aggressiveness and/or to protect plants against their infection (Collinge *et al*., 2022; Sarrocco, 2023). In this wide research topic, several examples of beneficial organisms and information about their mechanisms of actions (details are described in the following sections) as well as of their efficacy in several pathosystems are available for the scientific community. Microbial biocontrol, including PGPR (plant growth promoting rhizobacteria), embraces several bacterial isolates, mainly collected from the rhizosphere, capable of repressing plant pathogens. Isolates belonging to the genera *Pseudomonas*, *Bacillus* and *Bulkholderia* are the most frequently studied bacteria developed as commercial BCAs thanks to their ability to exploit their antibiotic, competitive or inducing plant defence response abilities against several plant pathogens on different host plants (Pandit et al., 2022). Filamentous fungi including endophytes have received substantial attention as potential BCAs, and their abilities as outstanding competitors, producers of specialised (secondary) metabolites and inducers of plant defence responses against biotic and abiotic stresses point to their potential (Keller, 2019, Collinge et al., 2019, Latz et al., 2018). Indeed several, especially *Trichoderma* species, have been developed into commercial products (Collinge et al., 2022). Yeasts also represent fungal groups receiving increasing attention also for their environmental adaptability that, coupled with several beneficial mechanisms of action they can exploit against plant pathogens, place them in a relevant position as active ingredients of biocontrol solutions to be used post-harvest (Sarrocco and Vannacci, 2018).

BCA solutions to control *fusarium* diseases on cereals

Many potential BCAs have been identified in laboratory studies and are under investigation with the aim to understand how they can prevent and/or counteract the negative effects of plant diseases. However, the process to develop a single beneficial strain in an effective formulation and introduce this to the market as a commercial BCA product is a time consuming and expensive process (Collinge et al., 2022). Of course, the process of product development varies from one country to another mainly due to different legislation. According to Collinge et al. (2022), readers are kindly invited to read the review by Stenberg et al. (2021) for a clear definition of biological control versus extracts and the umbrella concept of "bioprotectants".

Many BCAs are already on the market, especially in regions where there is a low legislative burden regulating their introduction, and it can be expected that this trend will continue. According to the “Global Biocontrol Agents Market Growth, Share, Size, Trends and Forecast (2023 – 2029)”, in the year 2022 the global biocontrol agent market – including not only (micro)organisms to be used against plant pathogens, but also products designed for pest management – was valued at USD 4.5 million (M€ 4), and this is predicted to increase to USD billion 11 (B€ 10) by the year 2029, thus corresponding to a compounded annual growth rate of 14.3%. This trend is justified, at least at a European level, by the need to reply to the “Farm to Fork” strategies that targeted to reduce, by 2030, the overall use and risk of chemical pesticides by 50% and the use of more hazardous pesticides by 50% (https://ec.europa.eu/food/sites/food/files/safety/docs/f2f_action-plan_2020_strategy-info_en.pdf).

The recent increasing trend of commercial biocontrol agents is exemplified by *Trichoderma* isolates. This genus includes the highest number of BCAs among all the other fungal genera and, according to Woo et al. (2023), commercial *Trichoderma*-based products in 2022 resulted in around 150 registrations, compared to around 20 reported in 2014 at a global level.

Despite this constant increase of registered products, the number of commercial biocontrol isolates developed for cereal cultivation is not very high. According to Collinge et al. (2022), who reported a list of commercial biocontrol products, only *Pseudomonas chlororaphis* MA342 (active ingredient of Cedomon® and Cerall®) has been registered as seed dressing BCA to control seed-borne fungal diseases on cereals, included those caused by *Fusarium* spp. This is perhaps surprising since, at the research level, several fungi and bacteria are under investigation, as single inoculants or in combination, to control *Fusarium* diseases in cereals. Fungal isolates belonging to the genus *Trichoderma*, as well as those of the species *Clonostachys rosea* are among the most studied and effective in controlling *Fusarium* diseases in wheat and other cereals. For example, *Trichoderma gamsii* T6085 has been studied for the last twelve years as a biocontrol agent against FHB in wheat (Matarese et al., 2012). This isolate exploits several modes of action to control *F. graminearum*, i.e. it acts as a direct competitor (Sarrocco et al., 2019a, Sarrocco et al., 2021a, Lasinio et al., 2021) as well as an inducer of host defence responses, being an endophyte of both wheat roots and spikes (Vicente et al., 2020, Sarrocco et al., 2021a, Risoli et al., 2023). Genome sequencing of T6085 has allowed the study of the molecular crosstalk occurring between the beneficial isolate and the pathogen (Baroncelli et al., 2016), thus paving the way to deep investigations of the molecular mechanisms regulating the beneficial effect of this isolate (Zapparata et al., 2021). In addition, the success of T6085 is also due to the huge amount of specialised metabolites it can produce (Vicente et al., 2022).

With respect to *C. rosea*, studies with the strain IK726 are undoubtedly the most fruitful in terms of results. After several investigations aimed to demonstrate its ability as BCA against several plant pathogens (Jensen et al., 2017, Jensen et al., 2022), IK726 has been shown to be an effective candidate for the control of FHB and promising for reducing mycotoxins in wheat and other cereals in the field. This has been evaluated in several GEP field experiments since 2012 (Jensen, DF, unpublished data). Studies have also shown that IK726 exploits several mechanisms of action, including the ability to detoxify the important *Fusarium* mycotoxin zearalenone (Kosawang et al., 2014a, Kosawang et al., 2014b). The genome of IK726 has been sequenced and compared with those of other *C. rosea* isolates (Karlsson et al., 2015). In addition, this strain can control FHB pathogens and the associated mycotoxin content both in wheat and other cereals (Jensen et al., 2022, Khairullina et al., 2022, Khairullina et al., 2023) and to tolerate the presence of phenazine and fungicides (Kamou et al., 2016, Karlsson et al., 2015) as the result of an efficient ABC-transporter system (Dubey et al., 2014). All these features characterising both IK726 and T6085 are not only very promising, but also suggests the option of combining the use of the two strains (Collinge and Sarrocco, unpublished results).

T. gamsii isolates have been demonstrated to control also crown rot and symptoms both alone (Stummer et al., 2020), both in combination with a *T. harzianum* isolate (Stummer et al., 2022) and with the bacterium *Pseudomonas azotoformans* (Makhlouf et al., 2023). The combination of *Trichoderma* and a bacterial strain appears to be a winning strategy and several authors investigated the possible combined treatment to control *Fusarium* spp. in wheat, as in the case of *T. asperellum* (Karuppiah et al., 2019), *T. atroviride* co-cultivated with *Bacillus amyloliquefaciens* (Karuppiah et al., 2020) and *T. atroviride* co-inoculated with *Bacillus subtilis* (Liu et al., 2022).

With respect to other *Fusarium*-cereal pathosystems, Galletti et al. (2020) described two *T. gamsii* isolates as being able to modulate plant defence responses against *F. fujikuroi* in maize. *T. asperellum* strains have also been described as potential biological control agents against the same pathogen (Cuervo-Parra et al., 2022).

Even though isolates of *Trichoderma* spp. and *Clonostachys rosea* appear to be the most used BCAs of *Fusarium* spp. affecting cereal production, other fungal species – such as *Penicillium* and *Sarocladium* have also been investigated recently as potential BCAs. *P. olsonii* ML37, an endophytic strain isolated from wheat (Latz et al., 2020), can colonize wheat spikes and transiently activate plant defence mechanisms associated with a reduction in FHB symptoms and significantly lower levels of the *F. graminearum* metabolites 15-acetyl-DON and culmorin (Rojas et al., 2022, Rojas et al., 2020). Among endophytic fungi, isolates belonging to the genus *Sarocladium* appear to be very promising as BCAs against FHB in wheat, as demonstrated previously (Rojas et al., 2020, Comby et al., 2017, Kemp et al., 2020).

Several examples of beneficial bacterial isolates have been reported over time as potential BCAs to be exploited in the management of *Fusarium* diseases on cereals, in addition to the already commercialised *Pseudomonas chlororaphis* MA342. *Lactobacillus plantarum* SLG17 and *Bacillus amyloliquefaciens* FLN13, applied as BCAs starting from the heading period until anthesis of wheat plants, have been described as promising agents for the reduction of FHB severity (Baffoni et al., 2015). The ability of *Bacillus subtilis* RC 218 and *Brevibacillus* sp. RC 263 to reduce DON accumulation in wheat and of *Bacillus amyloliquefaciens* and *Microbacterium oleovorans* to control *F. fujikuroi* growth and fumonisin accumulation at pre-harvest stage in maize have been reported (Chulze et al., 2015). *B. velezensis* RC 218 and *Streptomyces albidoflavus* RC 87B are able to reduce FHB symptoms and DON accumulation on *Triticum turgidum* var. *durum* under field conditions (Palazzini et al., 2018a). The same isolates also showed tolerance to triazole-based fungicides, thus giving an added value to their future development as BCAs (Palazzini et al., 2018b). Spray inoculation of lactic acid bacteria – such as *L. amylovorus* DSM20552 – to spikelets significantly reduced disease DON content in barley (Byrne et al., 2022). An interesting approach was described by Deroo et al., (2022) who introduced an alternative workflow for the discovery of novel bacterial BCAs in wheat against FHB based on the enrichment of wheat spikes by four distinct microbial communities in the presence of *F. graminearum* that reduced the infection pressure in the spike phyllosphere. Also in maize, the bacterial *Bacillus gibsonii* and *Brevibacterium frigoritolerans* were investigated as growth promoters and to ameliorate the negative effects of *F. moniliforme* (Batool et al., 2019), while the consortium of *Bacillus* sp. KFP7 and KFP17 reduced rice bakanae disease, caused by *Fusarium fujikoroi* (Nawaz et al., 2022).

Reduction of disease incidence and disease severity

Several modes of action have been described for beneficial isolates harnessing pathogenic features of *Fusarium* affecting cereals. However, from a practical point of view, the real success of their application should be a significant reduction of disease symptoms and, consequently, of mycotoxin contamination in order to assure optimal crop yields and food security. As far as we know, a considerable body of literature is available concerning greenhouse and field trials aiming on the reduction of disease index (DI) and disease severity (DS), the effect of the inoculation of bacterial and fungal isolates, in some cases with valuable results. *T. gamsii* T6085 inoculation onto wheat spikes at anthesis in the field resulted in 40-50% reduction of DI and 15% reduction of disease severity (DS) of FHB during the cropping season 2010-2011 (Sarrocco et al., 2013). The same isolate, when inoculated both on spikes and on soil (to favour crop residues colonization), caused a significant reduction of FHB (DI) and DS at 28 days post inoculation of T6085 in 2018-2019 trials (Alukumbura et al., 2022). Other *Trichoderma* isolates gave interesting results in terms of management of *Fusarium* diseases on cereals (Modrzewska et al., 2022). Hence, *T. harzianum* T22 was used to control *F. graminearum* resulting in a significant reduction of both DI and DS of around 60% and 30% in greenhouse (Foroutan, 2013), whereas *T. afroharzianum* used to inoculate wheat flowers, gave up to 70% reduction of area under the disease progress curve of FHB, caused by *F. culmorum* (Bouanaka et al., 2021). An average reduction by 36% of Fusarium ear rot caused by *F. fujikuroi* in maize was demonstrated when *T. harzianum* was used for seed priming (Ferrigo et al., 2020). Potential native *Trichoderma* strains have been tested against *F. fujikuroi* causing post flowering stalk rot in winter maize and *T. harzianum* BThr29, *T. asperellum* BTas25, and *T. erinaceum* BTer43 reduced DS from 18 to 62% in the field (Jambhulkar et al., 2022).

Equally interesting and promising results have been obtained in terms of disease control when *C. rosea* was used (Jensen et al., 2022), where a 70 % *F. graminearum* biomass reduction was reported using isolate IK726, coupled with DON level reduced in wheat under greenhouse conditions. When the same strain was inoculated at different concentrations on barley and wheat seeds in the field to control Fusarium crown rot (Fig. 2), the disease levels (DS) caused by *F. culmorum* were significantly reduced by 35-54% and by 37-68%, respectively, compared to infected controls (Jensen et al., 2000). A significant reduction of FHB index (around 50%) was obtained by using

Fig. 2 Application of *Clonostachys rosea* IK726 on wheat under field conditions. Mid front plot shows treatment with *Fusarium culmorum* alone, mid-centre is treated with IK726 + *F. culmorum* © Inge MB Knudsen reproduced from Jensen et al. (2007)

C. rosea strain ACM941 as a BCA both under greenhouse and field conditions (Hue et al., 2009) while a reduction of Fusarium damaged kernels by 31–39% was observed in grains (Xue et al., 2014). The effects were numerically lower, but not significantly different from those of the fungicide tebuconazole used in the same trials.

Regarding other fungal isolates, the endophytes *Anthracocystis flocculosa* (syn *Pseudozyma flocculosa*) P1P1 and F63P, *Sarocladium strictum* C113L and *Penicillium olsonii* ML37 were inoculated onto wheat spikes in greenhouse trials, and FHB severity caused by *F. graminearum* reduction ranged between 70% and 80% (Rojas et al., 2020). The biocontrol yeast *Aureobasidium pullulans* significantly contained the development of FHB (DS reduced by 20%) in winter wheat also in greenhouse trials (Wachowska & Głowacka, 2014). A mix of *Papiliotrema flavescens* (syn. *Cryptococcus flavescens*) and *Cryptococcus aureus* resulted in a significant reduction (32.0%) of DS under greenhouse conditions (Schisler et al., 2011).

Regarding other fungal isolates, the endophytes *Anthracocystis floculossa* (syn *Pseudozyma flocculosa*) P1P1 and F63P), *Sarocladium strictum* C113L and *Penicillium olsonii* ML37 were inoculated onto wheat spikes in greenhouse trials, and FHB severity caused by *F. graminearum* reduction ranged between 70% and 80% (Rojas et al., 2020). The biocontrol yeast *Aureobasidium pullulans* significantly contained the development of FHB (DS reduced by 20%) in winter wheat also in greenhouse trials (Wachowska & Głowacka, 2014). A mix of *Cryptococcus flavescens* and *Cryptococcus aureus* resulted in a significant reduction (32.0%) of DS under greenhouse conditions (Schisler et al., 2011).

With respect to bacterial inoculation*, Bacillus gibsonii* and *Brevibacterium frigoritolerans* were investigated for their potential to enhance growth and ameliorate the negative effects of *F. moniliforme* in maize, resulting in 67% disease reduction (Batool et al., 2019), while *Burkholderia cenocepacia* was able to significantly suppress maize root rot caused by *F. temperatum* on four cultivars during a greenhouse study (Tagele et al., 2019). *Bacillus megaterium* reduced FHB incidence and severity by 93% and 54%, respectively and DON contamination by 89.3% under field conditions (Pan et al., 2015), while *B. velezensis* RC 218 and *Streptomyces albidoflavus* RC 87B effectively reduced DI up to 30% and DON accumulation up to 51%) in durum wheat under field conditions (Palazzini et al., 2018a).

Interesting results have been obtained field conditions also by using beneficial organisms for the control of bakanae disease on rice. The antagonistic *Bacillus* sp. KFP7 and KFP17 significantly reduced disease incidence (≤25%) compared to plants infected with the pathogen *F. fujikuroi* (≥75%) in two rice cultivars, with an efficacy comparable to that of fungicide (Nawaz et al., 2022).

Modes of action of BCAs and their role in the control of *fusarium* diseases in cereals

The success of the use of BCAs in the management of plant diseases is mainly due to the combination of a range of modes of action they can count on in order to reduce the growth of plant pathogens as well as to prevent/counteract plant infection (Jensen et al., 2016, Jensen et al., 2017). From a general point of view, these modes of action can be grouped into two main categories, *i.e.*, direct and indirect, based on the fact that they can be effective directly against the pathogen or occur without physical contact between the BCA and the pathogen. The latter also includes resistance mediated by the plant (Köhl et al., 2019, Latz et al., 2018). Direct effects were close contact is required include hyperparasitism, where the BCA behaves as predator that can gain nutrients from its prey (the pathogen); antibiosis, where specialised (secondary) metabolites produced by the BCA negatively affect the growth, the development and/or the metabolic activity of the pathogen (Köhl et al., 2019; Collinge et al., 2022); and interference competition based on an antagonistic combat via direct contact or via antibiosis, to allow the BCA to control the access to food and monopolize the habitats (Sarrocco et al., 2019a). The indirect modes of action include exploitation competition, where the biocontrol agent reduces resource availability to the pathogen without the need of a contact between the two organisms (Sarrocco et al., 2019a). The modulation of plant defence responses – also defined as induced resistance (Sarrocco, 2023) – comprises the induction of plant defence mechanisms against invading pathogens (Conrath et al., 2015, Köhl et al., 2019, Collinge et al., 2022).

Within the context of biocontrol of *Fusarium* diseases in cereals, practically all the previously described modes of action can be successfully used by the BCAs in order to inhibit pathogen growth, to reduce host infection and to prevent disease development and, consequently, mycotoxin contamination. With respect to hyperparasitism, *T. gamsii* T6085 has been demonstrated to be able to coil *F. graminearum* mycelium, resulting in the death of the pathogen (Matarese et al., 2012). *C. rosea* IK726 has been investigated as a mycoparasitic isolate capable of inhibiting the growth of several plant pathogenic fungi, including the causal agents of FHB *F. graminearum* and *F. culmorum* (Karlsson et al., 2015, Jensen et al., 2022), while some *Pythium* spp. strains, isolated from straw pieces previously treated with the mycotoxin DON, were able to coil *F. graminearum* macroconidia and to affect their ability to germinate (Sarrocco et al., 2012).

The antibiotic activity of several BCAs involved in the control of *Fusarium* spp. affecting cereals has also been demonstrated. The production of the antifungal polyketide clonorosein A-D plays a role in the antagonistic activity of *C. rosea* IK726 against *F. graminearum* (Fatema et al., 2018),while a *T. asperellum* isolate showed antifungal activity against four species of phytopathogenic fungi including *F. fujikuroi* and *F. tricinctum* (Win et al., 2021). Among beneficial bacteria, *B. amyloliquefaciens* S76-3 isolated from diseased wheat spikes exerted a strong antagonistic activity against *F. graminearum* by producing the cyclic lipopeptides iturin and plipastatin (Gong et al., 2015a), while fengycin and surfactin lipopeptides produced by *B. mojavensis* RRC101 inhibited the growth of *F. fujikuroi* whose hyphae showed distortions, vacuolization and lysis (Blacutt et al., 2016).

Competition for nutrients and space has been reported in several papers focussing on the characterization of potential BCAs to be used for the control of fusariosis on cereals (Sarrocco et al., 2019a). The Biolog phenotype microarrays system has been used to analyse nutrient fungal utilization in a model system including the beneficial isolate *T. gamsii* T6085 and four causal agents of FHB (*F. graminearum, F. culmorum, F. langsethiae* and *F. sporotrichioides*), thus providing ecological information about which substrate one isolate prefers compared to the others, which is useful information to be exploited in biocontrol strategies (Lasinio et al., 2021). *T. gamsii* T6085 also showed exploitation competitive ability to colonize natural substrates, such as wheat and rice kernels, against *F. graminearum* (Sarrocco et al., 2019b).

The ability of *C. rosea*, *T. gamsii* T6085 and *Microsphaeropsis* spp. to compete with *F. graminearum* for wheat straw possession was observed, resulting in significantly reduced perithecial development (Bujold et al., 2001; Schöneberg et al., 2015; Sarrocco et al., 2021).

Transcriptomic approaches have been fruitful in elucidating aspects of crosstalk between a BCA and pathogenic *Fusarium* isolates. Thus, according to Zapparata et al., (2021) the a modulation of genes involved in iron uptake occurred during the sensing phase (at distance) between *T. gamsii* T6085 and *F. graminearum*, with an up-regulation of the expression of a ferric reductase involved in iron acquisition in the beneficial isolate and a down-regulation of gene encoding for proteins where iron plays a role. After hyphal contact between *C. rosea* ACM941 and *F. graminearum*, the beneficial isolate predominantly transcribed genes encoding cell wall-degradation enzymes as well as carbon source utilization pathways while the pathogen activated the transcription of phosphate starvation pathway signature genes (Demissie et al., 2020). When the biotrophic mycoparasite *Melanospora mycoparasitica* (syn. *Sphaerodes mycoparasitica*) was used in a transcriptomic and proteomic study in presence of *F. graminearum,* cell wall-degrading glucanases and chitinases were upregulated (Kim and Vujanovic, 2021).

It is well established that pathogens induce host defences, *i.e.,* PTI – pattern-triggered immunity. *Fusarium* spp. are no exception, and defences are induced both during the initial, biotrophic, stages of infection and the later necrotrophic stage (Brown et al., 2017, Yang et al., 2010). Although beneficial microorganisms have been well known for their ability to trigger systemic induced resistance against pathogens, the function and mechanisms underlying the induced responses in controlling *Fusarium* diseases remain to be understood (Nguvo & Gao, 2019). Colonization of maize with *T. harzianum* increased resistance to *F. graminearum* through activating the ethylene pathway (Molinari et al., 2014, Saravanakumar et al., 2018). In addition, the activation of the JA/ET signalling pathway after fungal infection of maize roots enhanced phytoalexin accumulation in leaves, thereby inducing the resistance to a broad spectrum of leaf pathogens (Saravanakumar et al., 2016). Two *T. gamsii* isolates inoculated on maize seeds modulated the expression of defence-related genes against *F. fujikuroi* (Galletti et al., 2020). Similarly, inoculation of *T. gamsii* T6085 on wheat roots and spikes significantly enhanced the expression of defence-related genes, such as *Lox1*, Pal1, *Pgip2* and *Pr1*, in roots, leaves and spikes (Risoli et al., 2023).

Endophytic root colonization is generally considered as a prerequisite to establishing cross-talk that can result in a positive response, in terms of growth stimulation and modulation of resistance in the hosts (Macías-Rodríguez et al., 2020). It is becoming increasingly clear that endophytic fungal biological control agents can also induce defences (Latz et al., 2018), and these include fungal BCAs isolated from rhizosphere and endopshere, including the phyllopshere. For example, the study of transcriptomes of BCA-treated systems provides evidence of induced resistance as mechanisms of FBH control by *Clonostachys rosea* in oat (*Avena sativa*) (Khairullina et al., 2023) and by *Penicillium olsonii* in wheat (Rojas et al., 2022). Induction of *pal1* expression in response to *Trichoderma* root colonization has already been reported in maize plants treated with *T. virens* (Djonovic et al., 2007), as well as with *T. harzianum* in response to Fusarium ear rot disease (Ferrigo et al., 2020). Inoculation and colonization of oat spikelets at anthesis with *C. rosea* IK726 activated expression of genes encoding four PR-proteins and a WRKY23-like transcription factor, suggesting that this beneficial isolate may also induce resistance in oat (Khairullina et al., 2023). A newly explored biocontrol mechanism in *C. rosea* is its possible ability, through RNA interference, to hijack regulatory mechanisms of the *Fusarium* prey and thereby obtaining a competitive advantage over this pathogen in hyperparasitic interactions – i.e. in biocontrol interactions (Piombo et al., 2021, Piombo et al., 2022).

Interactions among *fusarium* species and the reflection on BCAs activity

Many studies have demonstrated the presence of several *Fusarium* species and the related *Microdochium nivale* and *M. majus* -as commonly included in the fungal complex causing FHB (Oerke et al., 2010, Nielsen et al., 2011, Karlsson et al., 2017). Some of these are responsible for both severe disease symptoms and mycotoxin contamination of grains, as in the case of *F. graminearum* and *F. culmorum.* Conversely, infection by *Microdochium* spp., whilst damaging in terms of yield loss, does not result in mycotoxin contamination (Gavrilova et al., 2020). On the other hand, for example infection with *F. langsethiae* results in huge contamination with T-2 and HT-2 mycotoxins even if disease symptoms are limited (Imathiu et al., 2013).

Due to the wide number of species co-occurring on wheat, FHB represents a fascinating ecological example of fungal interactions where individuals can be involved in synergic or competitive relationships with a direct reflection on their ability to colonize the host, driving which species predominate and which are secondary, to develop disease symptoms and to produce mycotoxins (Xu & Nicholson, 2009, Karlsson et al., 2015). For example, *F. graminearum* was demonstrated to be the most competitive species in wheat and, consequently, mostly responsible for trichothecene accumulation, whereas *F. poae* was less competitive (Xu et al., 2007a). However, to confirm the complexity of the ecological features of these species, sometimes the weakly pathogenic *F. poae* thrives on the infection sites of the virulent *F. graminearum.* According to Tan et al. (2020), FHB symptoms disappeared, and mycotoxin levels were reduced, when *F. poae* was inoculated on wheat ears before *F. graminearum*, thus hypothesising that timing of infection can drive symptom development in the presence of these two species. When co-inoculating with *F. graminearum*, *F. poae* increases its growth as if taking advantage from the presence of *F. graminearum* and, even in the absence of symptoms related to its infection, plants inoculated with the weak pathogen *F. poae* show a modulation of their defence response, particularly that involving salicylic and jasmonic acid signalling, thus resulting in a delay in *F. graminearum* infection.

This multi-species nature of the Fusarium head blight and the complexity of the relationships, as well as the succession of its causal agents, has a prominent influence on its management, thus implying that different species could manipulate the effectiveness of the applied BCAs (Tan et al., 2021). This is particularly evident with actinobacteria, that, thanks to their versatility in using several beneficial mechanisms of action, such as hyperparasitism, production of antibiotics and lytic enzymes and their reservoir of specialised metabolites, are considered promising and efficient BCAs also against FHB (Palaniyandi et al., 2013, Newitt et al., 2019). In addition, they can also exert an indirect positive effect on the plant by activating defence pathways (Vergnes et al., 2020). However, despite the intriguing features of these microorganisms as BCAs, the effectiveness of *Streptomyces rimosus* strain LMG 19352 and of *Rhodococcus* sp. strain R-43120 to reduce FHB and concomitant mycotoxin levels in wheat due to *F. graminearum* infection depends on the presence or absence of *F. poae* in the ear. Even if able to significantly contain *F. graminearum* infection, when co-inoculated with the weaker pathogen (*F. poae*) and the more aggressive pathogen (*F. graminearum*), both BCAs showed significantly reduced biocontrol capacity, which shows that the presence of *F. poae* hampers the biocontrol of *F. graminearum* (Tan et al., 2021). The message from this study is that biological strategies aimed to control diseases caused by multiple fungi, such as FHB, might be more complex and difficult than expected. In the context of tri-partite interaction (pathogens/host/BCAs), an intricate network forms weave synergistic as well as competitive interactions, thus adding another level of complexity on the efficacy of BCAs in the management of *Fusarium* diseases.

Interactions between BCAs and the plant microbiome

Within the FHB complex on wheat, interactions with the plant microbiome play an important role in terms of general plant response as well as on the effect *Fusarium* community can exert on its host. It is well known that the plant can harbour bacterial and fungal populations, not only in the rhizosphere, but also in all aerial plant parts (i.e the phyllosphere), a complex microbial community is often defined as the phytobiome (Leach et al., 2017, Karlsson et al., 2021). This sophisticated ecosystem is regulated and driven by highly specific interactions including competition, predation, mutualism and symbiosis and directly affected by environmental conditions such as soil composition, temperature, humidity and water availability. This networking communication is also regulated by chemical and physical exchanges that allow us to talk about a real "make-up" of the phytobiome itself, mainly controlled by the plant (Leach et al., 2017, Sarrocco, 2023). Theoretically, it should be possible to manage the microbial community in order to improve the control of *Fusarium* diseases in cereals by manipulating or by applying the microbiome naturally associated with a healthy host plant.

Historically, the biocontrol of plant pathogens has been managed following the "silver bullet" concept, where a strategic management of the disease was explained as the result of the mechanisms of action of a single BCA (Sarrocco, 2023). However, considering that the success of BCAs is also achieved through indirect mechanisms, *i.e.*, by the response of the plant where a modulation of its defence response occurs (Pieterse et al., 2014), the role of the microbiome in this relationship appears to be of great importance in terms of disease control. Even if not fully applied within the context of FHB (Karlsson et al., 2021), starting from the demonstration a microbiome is able to transfer resistance to a pathogen from one host to another (Zahn & Amend, 2017), microbiome manipulation represents a valid approach to promote disease suppression by natural occurring communities. In the case of FHB, in view of the disease cycle where cultural debris and spikes at anthesis play a crucial role in the survival of the pathogens and for the infection of the host, respectively (Parry et al., 1995), the indigenous communities inhabiting soil and spikes, as well as the endophytic community (Latz et al., 2021, Rojas et al., 2020) represent a precious source of beneficial isolates to be used as BCAs. Seeds, leaves and roots are a reservoir of fungal communities, since they can harbour several populations that can be differently affected by the environment, as demonstrated by a wide metabarcoding analysis performed on wheat (Latz et al., 2021). Knowledge of factors naturally shaping the microbiome is required to evaluate better the efficacy of microbial BCAs. These kinds of observations can have practical implications in an agricultural context, particularly in the aerial part of the plant host, since the phyllosphere microbiome is shaped by the air microbiome to a large extent (Latz et al., 2021). It has been demonstrated that the lack of success of the efficacy of a BCA could be related to the composition of microbial community naturally associated with the host plant, since a BCA can perform better in the presence of the native microbial communities (Massart et al., 2015, Jensen et al., 2017).

Recently, the application of the beneficial isolate *T. gamsii* T6085 to spikes under field conditions was followed by a time-course sampling of the heads in order to analyse, by a metagenomic approach, the effect of the T6085 on the naturally occurring bacterial and fungal community (Alukumbura et al., 2022). This work, in addition to demonstrating that the BCA did not change the microbiome already present on the plant significantly – important information in view of the preservation of the biodiversity in response to the use of BCAs – suggested that several other taxa could be explored as potential biocontrol agents to integrate with T6085 treatment. However, the *Fusarium* spp. causing FHB appear to have learned the lesson that they should attack with perfect timing when the wheat is flowering. This provides the advantage of priority colonization (response trait) leading to infection and disease (effect traits) of being first. This fact is crucial for a biocontrol strategy where a single BCA introduction at flowering with a high dosage of the BCA can result in biocontrol as the priority effect (Jensen et al., 2017). Based on that, it appears relevant to focus on BCAs that already have shown effects in biocontrol of FHB instead of having the main effort on looking for new strains with unknown biology.

Challenges ahead for exploitation of microbiomes and understanding biological control

Because the plant microbiome is important for plant health, productivity and environmental adaptation (Fitzpatrick et al., 2018), microbiome manipulation is in focus as a viable route for sustainable agriculture (Afridi et al., 2022). This can be via synComs (synthetic communities), combinations of two BCAs, or epigenic regulation. Plants have co-evolved with microorganisms, resulting in an evolutionary selection of plant adaptability to their environment and its dynamic course. In terms of soil microbiota, rhizobia, AMFs and PGPR are examples of successful interactions that are primarily controlled by specific receptors. In barley, RLK4-RLK10, belonging to NFR1 and NFR5 families, a complex of receptors activating root nodule organogenesis has been described (Rübsam et al., 2023). When it is applied in *Medicago truncatula* complexed with nanoparticles, it can induce nodulation even if no infection appeared after inoculation with the rhizobium *Medicago loti*. Nitrogen fixation activity in rice has also been studied in paddy field conditions, where cyanobacteria and heterotrophic bacterial diazotrophs showed a positive balance (Ladha et al., 2016). Despite this, the composition and role of the microbiome is extremely plastic particularly in cereals. Its dynamics varies depending on the plant (organs, tissues, age), as well as the environment (Gdanetz and Trail, 2017, Latz et al., 2018). As a result, microbiome manipulation is as intriguing as challenging as a new frontier in plant disease management. Plant microbiome studies also have the side advantage of directly screening for antagonists in healthy plant growing where the disease is an issue (Collinge et al., 2019). *Pseudomonas piscium* ZJU60, isolated from wheat field samples, is one of the most recent examples. Its activity induces suppression of pathogens growth, virulence and mycotoxin biosynthesis in *F. graminearum* through fungal histone manipulation (Chen et al., 2018). Similarly with endophytic fungi isolated from healthy wheat under *Fusarium* pressure (Rojas et al., 2022, Rojas et al., 2020). While microorganism engineering is not currently a realistic strategy in many, especially European countries, plant breeding to produce plants that are more susceptible to microbiome interaction and selection appears to be a viable approach for investigation, although perhaps not easy, considering where the microbiome is recruited from (Latz et al. 2021).

Moreover, the “cry for help” hypothesis has shown that plants are able to select their own soil microbiome spatially and temporally (Haas & Défago, 2005, Sarrocco, 2023). This evidence has been thoroughly investigated over the last few decades in order to find suitable translation in applicable tools. Synthetic microbial communities (SynComs) are an intriguing opportunity as they can exert protecting activity involving host mediation against biotic stress (Vannier et al., 2019). SynComs are designed to most closely resemble the natural microbiome in composition and in function and it has been possible to assemble a SynCom comprising up to 200 microbial isolates (Li et al., 2019, Wang & Song, 2022). However, many challenges lie ahead, not least determining how to ensure synthetic consortia are able to perform without deleterious effects on natural microbiomes to be included into the fragile rhizosphere equilibrium, and that it also has to be studied whether individual members of consortia inhibit each other.

BCAs can also be improved in performance by combining a few or by combining them with other types of bioprotectants or even with synthetic fungicides (Ons et al., 2020). In the future, the combined use BCAs could consider the different modes of action against the pathogen as well as at quality of interaction occurring between the selected BCAs. Thus, the quality of their interaction - synergic or antagonistic - has a different effect on the disease control, emphasizing the importance of preliminary deep investigation (Xu & Jeger, 2013). *Trichoderma* spp. has been shown to perform very well when co-inoculated with bacterial BCAs such as *Pseudomonas* spp. and *Bacillus* spp, showing a synergic interaction based on several mechanisms of action (Poveda and Eugui, 2022). Antagonistic interactions are more likely to occur than synergistic ones (Xu and Nicholson, 2009). In any case, a deeply structured combined use of BCAs may provide a way to customised commercial BCAs based on geographical and environmental conditions. However, companies may be hesitant to produce combinations since (depending on region) each component may have to be approved separately as well as all the possible combinations of the individual partners.

Epigenetic regulation of gene expression is an essential tool, developed by plants to resist under abiotic and biotic stress. In rice, epigenetic regulation of two NRL receptors PigmR and PigmS can balance high disease resistance to *Pyricularia oryzae* and yield crop (Deng et al., 2017). Plants can also mediate RNAi silencing through post-transcriptional silencing. Virus induced gene silencing has been used in wheat (*T. aestivum* cv. Apogee) to silence four *F. culmorum* genes putatively involved in the virulence process (*FcFgl1* secreted lipase; *FcFmk1* Mitogen-activated protein (MAP) kinase). FHB symptoms were significantly reduced and FHB resistance was even enhanced in leaf and spike under greenhouse conditions (Chen et al., 2016).

Concluding remarks

This paper reviews the considerable progress made in recent years in understanding the nature of the interactions between pathogenic *Fusarium* spp and fungal BCAs, in particular species of the genera *Trichoderma* and *Clonostachys*. Promising results using BCAs from these genera to control head blight and crown rot diseases on cereals caused by mycotoxigenic *Fusarium* species has been presented, and have also showed that, in some cases, they are able to reduce accumulation of mycotoxins in grains too. We have learnt much about how these fungi operate and how we can exploit them in practical crop production. We are not yet there but we are getting closer to the magic bullet: a BCA that controls Fusarium diseases efficiently and at the same time reduce mycotoxin contamination of harvested grain. Most probably, successful biological control of the Fusarium diseases will rely on the integration of BCAs in IPM strategies.

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