Fusarium diseases

biology and management perspectives

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Fusarium diseases: biology and management perspectives

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1 Introduction

Wheat and barley are crucial crops for world food supply and represent two of the most important agricultural commodities in temperate areas. World wheat production has averaged 632 million metric tonnes annually in the last 25 years, while barley production has remained constant at around 142 million tonnes (FAOSTAT). Fungal diseases directly affect crop productivity by reducing yield, but also affect the quality of cereals. A major problem is caused by a number of fungal species in the genus *Fusarium*. Fusarium head blight (FHB), also known as 'head scab' or 'wheat scab', and Fusarium crown rot (FCR), also known as 'seedling blight' or 'Fusarium root rot', are two diseases caused by *Fusarium* species in small-grain cereals. FHB is a late disease that occurs during flowering and kernel development, whereas FCR causes damping off following infection of the leaf sheaths, stem base and roots, mainly of seedlings and in early stage plants. Yield losses vary widely,

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but can reach up to 70%. However, the most important aspect of *Fusarium* diseases in small-grain cereals is the production of toxic specialized (or secondary) metabolites like trichothecenes, fumonisins and oestrogenic metabolites by the causal fungi. These are harmful toxins for livestock and humans: consumption poses an important health risk, especially in the long term.

The main strategy for the control of *Fusarium*-caused diseases in cereals is currently based on the premise of reducing inoculum to prevent initial infection. Traditionally, these measures are accompanied with the use of fungicides that reduce the rate of infection and result in lower mycotoxin accumulation. However, these actions do not guarantee consistent control, particularly against such an unpredictable disease as FHB. Simultaneously, agricultural practices such as reduced tillage and continuous cereal rotations that favour the disease are under increasing focus (Mangalassery et al. 2014; Gan et al. 2015). Likewise, an increase in average temperatures and more stochastic rainfall pattern caused by climate change would affect pathogen populations and could change the geographical patterns of disease epidemiology (Parikka et al. 2012).

Taken together, these factors could lead to major FHB outbreaks like those experienced early in the twentieth century. Moreover, overuse of chemical control will inevitably drive to the appearance of fungicide-resistant *Fusarium* strains. All these challenges require plant scientists and especially agronomists to update their knowledge about the disease and to rethink their management strategies. Understanding the biological mechanisms that govern the interaction between pathogens and plants can provide clues of the areas where this can be improved. In this chapter, we attempt to compile the recent findings on the *Fusarium*–cereal interaction, mode of infection and plant responses and analyse their implications in the development of complementary management strategies in the frame of integrated disease management.

2 *Fusarium* epidemiology and distribution

Fungal geneticists place the origin of the genus *Fusarium* around 91.3 million years ago in the middle Cretaceous as mainly wood saprophytes (O'Donnell et al. 2013). The genus saw a later explosion in diversity during the Miocene, coinciding with an increase in angiosperm diversity, thus explaining their strong association with plants (Watanabe et al. 2011). While *Fusarium graminearum* (teleomorph *Gibberella zeae*) has been reported as the predominant species in wheat and barley, other species play important roles in specific regions. These include: *F. culmorum, F. avenaceum, F. pseudograminearum, F. triticum, F. poae* and *F. asiaticum*, among others (Pasquali et al. 2016). Some of the most related species are grouped under the name of '*Fusarium graminearum* species complex' (FGSC) or *Fusarium graminearum sensu lato*. This complex includes the taxa: *F. acaciae-mearnsii*, *F. aethiopicum*, *F. asiaticum*, *F. austroamericanum*, *F. boothii*, *F. brasilicum*, *F. cortaderiae*, *F. gerlachii*, *F. graminearum sensu stricto*, *F. louisianense*, *F. meridionale*, *F. mesoamericanum*, *F. nepalense*, *F. ussurianum* and *F. vorosii* (Aoki et al. 2012) although not all are universally recognized. The geographical distribution of FGCS has shown that several species can co-exist (Nielsen et al. 2011). FGSC populations can have separate evolutionary dynamics in relation to different hosts and should be considered as a group of relatively independent populations that built a meta-population globally (van der Lee et al. 2015).

These variations in population dynamics are mainly driven by niche-competition with other pathogens, disease management practices, weed control and canopy humidity (Xu and Nicholson 2009) and by climatic conditions such as temperature, rainfall patterns and crop rotations (van der Lee et al. 2015). For example, it is often reported that *F. graminearum* is predominant in warm areas, whereas *F. culmorum* and *F. avenaceum* are more abundant in colder areas. This is partially true, but some of these patterns have been shifting in the last years with the introduction of maize in crop rotations (especially in Europe), the great adaptability of the *Fusarium* spp. and rising temperatures due to climate change (Kim et al. 2016). Nonetheless, some studies have shown that long-term rotations reduce disease levels, but do not affect *Fusarium* population composition infecting stem bases (FCR), implying a more resilient population structure (Tillmann et al. 2017). Recently, several mycotoxin-producing *F. graminearum* and other species were isolated from symptomless grasses in North American prairies (Lofgren et al. 2017). This is evidence of lifestyle plasticity of *Fusarium* spp., which colonizes most grasses as endophytes, but can be virulent in cereal crops. In general, the large intrinsic genetic variation of *F. graminearum sensu lato* should be taken into account when assessing FHB epidemiology since *Fusarium* populations are shaped by environmental factors as well as host availability.

3 Disease cycle and infection

The FHB and FCR disease cycles (Fig. 1) commence when rising temperatures in early spring initiate the production of saprophytic hyphae in crop debris. Under warm and moist conditions, sexual ascospores or asexual conidia are produced. Although some *Fusarium* spp. have a known sexual stage, many pathogenic species, including *F. cerealis*, *F. culmorum*, *F. equiseti*, *F. poae* and *F. sporotrichioides*, have no known sexual stage (Kerényi et al. 2004). Indeed, asexual spores are the main cause of infections in most cultivated areas. Three kinds of asexual spores are produced depending on the species: macroconidia are produced in sporodochia, microconidia are produced on conidiophores and chlamydospores are produced inside hyphae (Dweba et al. 2017). Furthermore, sexual ascospores, produced in perithecia, are also able to produce infection and their role in generating genetic variation is key in the pathogenicity of *Fusarium* spp. (Vanheule et al. 2017).

Splashing is the main means of initial infection for FHB (Osborne and Stein 2007). After landing on floret tissue, spores can colonize the external surface of the glumes or infect directly through stomata, exposed anthers and lemma-palea openings (Champeil et al. 2004). The fungus forms specialized structures such as compound appressoria and infection cushions to penetrate the floral bracts and the ovary/grain tissues (Boenisch and Schäfer 2011). Infection is higher under conditions of high humidity and temperature. Initially, fungal hyphae grow in the apoplast without causing any visible symptoms. They reach the rachis and spread to neighbouring spikelets in both basipetal and acropetal directions, but not through the vascular tissue (Brown et al. 2010). As the disease advances, colonized tissue dies and symptoms appear (Brown et al. 2010). Recently, it was shown that barley trichomes play a role in trapping conidia and offering infection sites, suggesting a potential resistance mechanism (Imboden et al. 2017). In wheat, the fungus colonises the spikelets, producing brown lesions on the glumes that quickly bleach the spikelets,

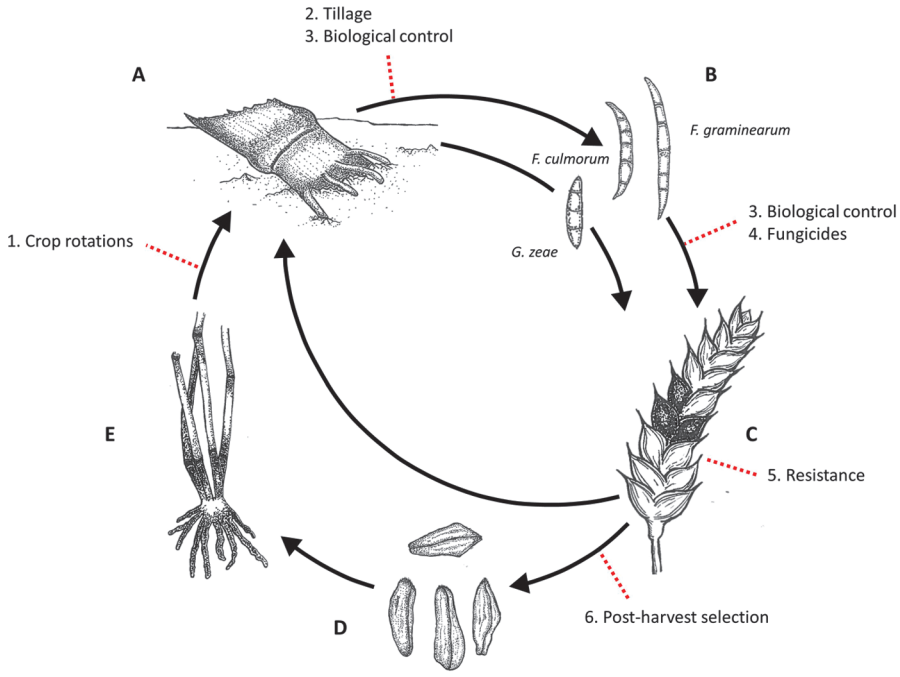

Figure 1 Disease cycle: A. Saprophytic phase on crop residues. B. Production of asexual macroconidia (*F. graminearum* and *F. culmorum*) or sexual ascospores (*G. zeae*). C. Infection of flowering spikelets and symptom appearance. D. Fusarium damaged kernels with mycotoxin contamination. E. Infected but visually acceptable grains can be used as seeds and may produce Fusarium crown rot on seedlings. Additional dotted lines represent points during the disease cycle where management strategies are able to disrupt the cycle: 1. Crop rotations are the best strategy for inoculum reduction. 2. Tillage can bury crop debris and reduce spore production. 3. Biocontrol agents on crop residues pre-sowing, applied to the head at anthesis or coated onto the seeds to prevent Fusarium crown rot are a potential control strategy. 4. Fungicide use at mid-flowering can reduce infection rates and severity, as well as mycotoxin accumulation. 5. Genetically resistant lines reduce initial infection, disease spread or mycotoxin accumulation. 6. Post-harvest grain selection can be performed adjusting combine harvester parameters or in storage facilities.

whereas in barley, these lesions can be dark or brownish which make real severity difficult to estimate (Janssen et al. 2018). In later stages of colonization, the spikelets turn pink or orange as the pathogen produces mycelia and synnema where conidia are produced over the necrotized tissue.

These spores and conidia can overwinter on crop residues, especially on tissues that do not degrade easily. Infected grains thus act as a disease vector when sown. These seeds germinate and may develop FCR. The infection in the crown area generates brown discoloured lesions on the coleoptiles and the roots which can turn black as they progress. In some cases, a pink/orange discoloration appears over the lower nodes due to production of spores (Scherm et al. 2013). This shows the great relevance of seed selection, as well as the use of agricultural practices in breaking the disease cycle. Likewise, it displays the crucial role of rainfall regimes as a driver of initial infection as well as a climatic variable.

4 Host–pathogen interaction

The interaction between *Fusarium* species and cereals is one of the most studied and important pathosystems in plant pathology (Dean et al. 2012). Full transcriptome analysis in the interactions between *F. graminearum* with cereals has been reviewed in depth recently by Kazan and Gardiner (2017). The fungal infection dynamics appear to be somewhat similar for both FHB and FCR. The fungus displays two phases: a biotrophic symptomless phase in which the fungus colonizes the intercellular tissue and a necrotrophic, symptomatic phase where the fungus degrades the infected tissue (Brown et al. 2017). However, its proven endophytic lifestyle and the latest findings at molecular level suggest a more complex interaction which raises questions about its ecology (Selosse et al. 2018).

Most studies have used *F. graminearum* as a model system for the interaction. It has been shown that during the first phase, fungal metabolism is entirely devoted to growth and plant response suppression. Several fungal proteins are secreted during this early phase (Yang et al. 2012). Fungal genes involved in transport, carbohydrate metabolism and detoxification are highly expressed during infection (Lysøe et al. 2011). Similarly, the production of extracellular siderophores such as TAFC (triacetylfusarinine C) and malonichrome has been shown to be activated during the first phase. These chelating molecules appear to play a role in coping with oxidative stress related to plant responses (Oide et al. 2014).

Likewise, the activation of genes involved in deoxynivalenol (DON) biosynthesis such as *TRI* enzymatic genes have been shown to increase during early stages. Interestingly, the production of DON has been shown to be activated by plant signals. Several polyamine compounds that are produced by the plant under infection activate DON biosynthesis in *F. graminearum* (Gardiner et al. 2009). Remarkably, the fungus appears to be able to hijack the plant metabolism to enhance DON production by activating the production of putrescine, a DON stimulator (Gardiner et al. 2010). Recently, it was shown that this mechanism is key for the sustenance of the biotrophic phase, as DON inhibits plant responses by binding to the small ribosomal units preventing protein translation (Brown et al. 2017). Many of the genes involved in DON production have been studied using reverse genetics, confirming the importance of genes like *Trichodiene synthase 5* (*Tri5*) in infection (Cuzick et al. 2008) and transcription factors such as *Tri6* and *Tri10* in pathogenicity (Jiang et al. 2016; Seong et al. 2009). Although important in enhancing infection, DON production is not vital for infection; either in heads (Jansen et al. 2005) or in seedlings (Powell et al. 2017).

During the necrotrophic phase, cell-degrading metabolism is primarily activated. Up to 50 Carbohydrate-Activated Enzymes (CAZymes) were found to be expressed during the interaction, but significantly increased during necrotic phase (Zhang et al. 2012). These enzymes have been shown to be activated during starvation and saprophytic lifestyle. This suggests that the shift of infection mechanisms may be regulated by nutrient deprivation during the biotrophic phase (Brown et al. 2017). Indeed, autophagy mechanisms used to maintain homeostasis in fungal cells and recycle nutrients were shown to be necessary for growth and pathogenicity (Lv et al. 2017). Furthermore, Brown et al. (2017) found that the expression of several effector genes were upregulated during infection and interestingly, this secreted protein cocktail appears to be specific for each phase and their location in the genome aligns with high recombination regions.

To put it briefly, the pathogen can regulate its pathogenicity during the biotrophic to necrotrophic transition and this appears to be modulated by host signals and requires a tight transcriptional reprograming in the fungus. The regulation involves plant response

suppression mechanisms, stress-tolerance metabolism, effectors, polysaccharides degradation enzymes and mycotoxin production (Brown et al. 2017).

Like other plant–pathogen interactions, *F. graminearum* infection has been associated with enhanced expression of genes involved in primary metabolism and defence reactions in the host. Chitinases, reactive oxygen species and peroxidases as well as pathogenesis-related proteins (PR proteins) were activated rapidly in wheat after infection (Ding et al. 2011; Khaledi et al. 2016). Similarly, transcription factors associated with pathogen interactions such as *WRKY* and *bZIPs* and protein kinases involved in signal transduction were also expressed during FHB (Erayman et al. 2015). This indicates that deployment of a rapid and strong activation of defence responses is associated with increased resistance.

When comparing highly susceptible cultivars with moderately resistant, transport and detoxification of virulence factors such as effectors, toxins and enzymes contribute to increased resistance. ABC transporters, glucosyltransferases, proteinases and protein inhibitors make part of a second layer of defence mechanisms that are differentially expressed in plants with different levels of resistance (Gottwald et al. 2012). These defence mechanisms are energetically expensive (Martinez-Medina et al. 2016). Primary metabolism and carbon cycle genes are among the most abundantly expressed in wheat after *Fusarium* infection (Erayman et al. 2015). These genes play a key role in metabolic reprogramming during defence activation and their regulation represents potential targets for new breeding programmes (Hulsmans et al. 2016).

Plant hormones have received relatively little attention in the study of *Fusarium*–cereal interactions and the findings are not straightforward to interpret. Early activation of the jasmonate pathway appears to be crucial in response to *Fusarium* infection and together with the salicylic acid (SA) pathway; it has been associated with defence responses in tolerant cultivars (Ding et al. 2011). In contrast, Li and Yen (2008) suggested that SA did not play a role in defence. Furthermore, ethylene metabolism has been shown to enhance FHB resistance, while other studies associate ethylene with higher susceptibility (Xiao et al. 2013). Similarly, gibberellic acid and abscisic acid were shown to have antagonistic roles in FHB resistance, as exogenous application decreased and increased FHB symptoms, respectively (Buhrow et al. 2016). In brief, the plant response to infection is active and it includes several chemical mechanisms in two basic layers of defence. The activation of these mechanisms depends strongly on complex and subtle plant-hormone regulation and on activation of primary metabolism reconfiguration.

5 Genetic resistance

The use of *Fusarium*-resistant genetic material would be the most efficient and environmentally safe control practice. However, effective resistance has remained elusive for both wheat and barley, and no race-specific resistance genes have been described. Thus, resistance to both FHB and FCR appears to be scattered among many genes across chromosomes (He et al. 2016). Moreover, these genes appear to be subject to strong genotype-by-environment interactions (He et al. 2016). More than 250 quantitative trait loci (QTLs) have been described to confer some level of resistance, but the vast majority remain to be validated in reverse genetics experiments (Jia et al. 2017). Five types of resistance are recognized: Type I: resistance to initial infection; Type II: resistance to infection spreading; Type III: resistance to kernel infection; Type IV: tolerance to reduced yield and quality losses and Type V: resistance to mycotoxin accumulation (Mesterhazy

1995; Wegulo et al. 2015). Similarly, cleistogamous (closed flowering) lines show less susceptibility to FHB infection in both wheat and barley (Kubo et al. 2010).

Some of the most important QTLs have been characterized for their mode of action. Most of them appear to confer Type II resistance and in some cases by combining several mechanisms. For example, QTLs *QFhb1* and *QFhb2* have been associated with increased defence metabolites from the phenylpropanoid pathway, as well as activation of the JA pathway and detoxification of DON to less toxic compounds (Kazan and Gardiner 2017). QTL *Qfhs.ifa5a* conferred Type I resistance by enhanced lipid transfer protein, although the mechanism is unclear (Schweiger et al. 2013).

Using both native and exotic genetic diversity sources, several breeding programmes have achieved certain levels of success. The Chinese wheat line Sumai 3 shows consistent FHB resistance and has been used extensively in breeding. Several QTLs combining both Type I and Type II resistance confer its resistance. Similarly, several QTLs associated with the activation of SA, jasmonic acid and ethylene have been shown to confer resistance in the cultivar Wangshubai (Jia et al. 2017). Recently, a pore-forming toxin-like protein (*PFT*), which encodes a chimeric lectin, was shown to be responsible for the QTL *QFhb1*-mediated resistance (Rawat et al. 2016). The biochemical mechanisms behind this QTL were thought to be due to DON inactivation (Niwa et al. 2014). However, *PFT* is not involved in DON detoxification. Instead, it has been suggested that it might act as an antifungal protein that increases membrane permeability in the pathogen (Rawat et al. 2016).

Efforts in Europe have described other interesting QTLs such as *Qfhs.ndsu-3BS*, which improved Type II resistance. In the USA, native resistance genes have been successfully fixed onto resistant *QFhb1*-donor cultivars (Eckard et al. 2015). In the case of FCR, three QTLs (*Qcrs.cpi-3B, Qcrs.cpi-5D* and *Qcrs.cpi-2D*) have been shown to be consistent in reducing severity up to 60% when introduced in susceptible populations using gene pyramiding (Zheng et al. 2017). So, although effective resistance is as yet unavailable, the results suggest great potential for gene pyramiding strategies in the future. A list of partially resistant cultivars has been summarized recently by Shah et al. (2017).

Introducing foreign genes via transgenesis to reduce FHB is possible (Collinge et al. 2016). The antimicrobial protein bovine lactoferrin was introduced in the susceptible wheat cultivar Bobwhite. This transgenic wheat showed 75% less FHB incidence when compared to untransformed cultivars (Han et al. 2012). Similarly, the gene *NPR1* from rye (*Secale cereale*), which regulates the activation of systemic acquired resistance (SAR), was introduced into highly susceptible cultivar Ningmai. Transgenic plants showed earlier and higher levels of expression of PR-genes and a significantly higher resistance than the wild type (Yu et al. 2017). Likewise, overexpression of the *Arabidopsis thaliana NPR1* gene in wheat was shown to reduce severity by activating the SA pathway (Makandar et al. 2012).

Although considerable progress has been made in developing partial disease resistance by conventional plant breeding, total resistance probably cannot be achieved by this route. Promising results have been obtained by transgenic approaches and we can predict that these will implemented in some regions in the not-too-distant future.

6 Mycotoxins

Fusarium fungi associated with cereal diseases produce mycotoxins. These are diverse, specialized metabolites including trichotecenes, especially DON, nivalenol (NIV), 3-acetyldeoxynivalenol (3-ADON), T-2 toxin, HT-2 toxin, as well as fumonisins and

oestrogenic metabolites like zearalenone (ZEA) (Lee and Ryu 2017). Some of them are toxins in animals and represent an important health risk when consumed. Specific *Fusarium* mycotoxins are associated with nausea, vomiting, diarrhoea, abdominal pain and fever and under constant exposure they have been linked to neurological disorders, immunosuppression and cancer (Antonissen et al. 2014). ZEA has a rather different effect; being an oestrogen homologue, it causes reproductive disorders in farm animals and hyperoestrogenic responses in humans (Hueza et al. 2014). Mycotoxin-contaminated grain as animal fodder can cause anorexia, reduce weight gain rates and cause reproductive disorders in swine and poultry (Döll and Dänicke 2011).

Among all *Fusarium* mycotoxins, trichothecenes such as DON and its acetylated derivatives have been widely studied. The biosynthesis of these compounds commences with the cyclization of farnesyl pyrophosphate, catalysed by the enzyme trichodiene synthase (*Tri5*), then it is modified through oxygenations (*Tri1*) and esterifications (*Tri16*) into DON (Boenisch et al. 2017). Individual isolates of *Fusarium* spp. can have different trichothecene profiles: specific gene expression patterns in the DON biosynthesis pathway (*TRI* genes) were observed during wheat infection with two *F. graminearum* strains with distinct chemotypes (Amarasinghe and Fernando 2016). It has also been shown that mutations in *Tri13* and *Tri7* genes can generate changes in chemotypes as these genes are involved in the conversion from DON to NIV and the acetylation of NIV to the more toxic 4NIV (Lee et al. 2002). However, DON remains the most common mycotoxin found in cereals. This confirms that DON production offers a fitness advantage when infecting cultivated cereals (Xu and Nicholson 2009) and can thus also be considered to be an (albeit weak) phytotoxin or virulence factor. Interestingly, a comparative genome analysis showed a richer genetic pool for the production of these secondary metabolites than previously estimated, as well as a capacity for horizontal gene transfer and other evolutionary mechanisms of diversification within the genus *Fusarium* (Ma et al. 2013). The occurrence of different mycotoxin chemotypes in harvested grains is directly related to the composition of *Fusarium* spp. in the population and it follows the same dynamics (Lee and Ryu 2017; van der Lee et al. 2015).

Many countries have legal restrictions on the permitted levels of mycotoxins, especially DON and ZEA in cereal-based products. The maximum permitted levels in the European Union (EU) are, for example, 0.75 ppm for DON and 0.075 ppm for ZEA, for flour, bran and germ for human consumption. Permitted levels for unprocessed wheat and barley are 1.7 and 1.5 ppm, respectively, for DON and 0.1 ppm for ZEA (European Commission 2006). There is no current legislation for NIV in the EU as NIV levels are closely related to DON (Nielsen et al. 2014). Mycotoxin detection methods are divided in two categories: immunochemical-based methods that allow a fast and simple screening of large number of samples. Several kits based on ELISA assays are commercially available and are included in most food safety protocols (Anfossi et al. 2016). Secondly, chromatography-based methods: these allow higher resolution of the mycotoxin profile, but require specialized personal to perform and interpret the results, and are consequently more expensive. These methods are often used as validation test to complement ELISA kits or to perform in-depth mycotoxin analysis (Capriotti et al. 2014). Mycotoxins are thermostable and remain in cereal products after processing (Antonissen et al. 2014), but contaminated grain can be removed to some degree during harvest by changing the fan speed and shutter opening in the combine harvester to reduce mycotoxin content significantly (Salgado et al. 2015). To sum up, mycotoxin production by *Fusarium* fungi is a key component of their survival and pathogenicity. They represent a present-day health threat in food chains that receives constant survey in the world.

7 Yield and quality losses

Mycotoxin contamination ultimately defines the price and purpose of the harvest since contaminated grains that surpass the maximum levels must be destroyed, while contaminated grain that does not exceed the permitted levels is at best penalized on its price in the market. Although growers assume most of the economic cost, higher prices and low quality costs are shared by grain traders, mills and bakers in the production chain. This makes total economic impact difficult to estimate. Annual average costs of FHB in wheat and barley in the USA has been estimated to approximately USD$27 million, representing 3.7% of the whole annual value of these crops (Nganje et al. 2004). Similarly for FCR, annual costs were estimated to be around USD$100 in Australia in both crops (Murray and Brennan 2010).

FHB yield losses have been assessed in multiple field studies. The values vary widely between 10% and 50%, depending on the weather conditions and *Fusarium* populations (Kikot et al. 2011; Xu and Nicholson 2009). Likewise, it has been shown that agricultural practices such as crop rotation, tillage, sowing date, fungicide treatment, cultivar, fertilizer source, irrigation regimes and overall production system (conventional vs organic) have an influence on the final DON concentration in both wheat and barley (Bernhoft et al. 2012; Wenda-Piesik et al. 2017). In the case of FCR, yield reductions can reach up to 26% in Australia and 50% in the USA (Liu and Ogbonnaya 2015). The grain yield reduction is mainly due to reduction in plant stand, and losses in kernel weight and other yield parameters are also important (Moya-Elizondo and Jacobsen 2016; Smiley et al. 2005). Additionally, it has been shown that Fusarium disease index and per cent of *Fusarium*-damaged kernels are two good indicators of DON concentration. However, since environmental variables largely affect DON levels, Fusarium disease index should not be used solely as a mycotoxin estimator (Paul et al. 2006). Recently, it has been shown that FHB total yield losses can be predicted using a linear mixed-model regression analyses to estimate the relationship between Fusarium disease index and yield parameters (Salgado et al. 2015).

Quality reductions in wheat are also associated to its diminished processing qualities. Mycotoxins were shown to reduce flour yield and brightness and most importantly, baking performance (Siuda et al. 2010). In the case of barley, effects of severe FHB are seen in the malting process. Reduced germination as well as deficient brewing parameters (gushing) and undesirable flavours have been associated with high levels of infected grains and DON concentrations (Oliveira et al. 2012). Recently, fungal biomass was correlated to low malt extract quality for both *F. poae*– and *F. langsethiae*–infected barley grains (Nielsen et al. 2014). This suggests that different mycotoxin levels, as well as final quality parameters, are affected by changes in *Fusarium* populations. Therefore, in addition to its potential health risks, FHB represents economic losses to farmers by reducing final yield. It also affects the industrial sector by reducing commercial quality parameters.

8 Disease management

8.1 Agricultural practices

Disease management in wheat and barley is based on agricultural practices that reduce the initial inoculum pressure. Crop rotations with non-cereal crops, especially avoiding rotations with maize, are the base of integrated management strategies, particularly in areas with soil-humidity limitations (Qiu et al. 2016). Stubble burning (outlawed in the EU for cereal crops)

or soil turnover through ploughing can also be used. These tillage operations can reduce disease incidence and severity as well as mycotoxin levels significantly (Scala et al. 2016). However, they may also lead to losses in soil quality parameters such as structure, porosity and moisture (Montgomery 2007) and therefore heavy-duty tillage operations are sometimes discouraged in intensive systems (Townsend et al. 2016) although they remain effective in reducing inoculum. In addition, it has been shown that avoidance of mineral fertilizer and herbicides can reduce the levels of DON in kernels, as these input factors can modify canopy microclimate by increasing humidity (Bernhoft et al. 2012). A decrease in nitrogen fertilization has also been shown to increase *Fusarium* infection in barley which suggests control of nitrogen fertilization as a possible way to minimise FHB in barley (Yang et al. 2010).

Remarkably, it has been shown that long-term rotations reduce disease levels, but do not affect *Fusarium* population composition, causing FCR (Tillmann et al. 2017). Likewise, other agronomical variables have been shown to be related to FHB. Delaying optimal sowing date by 20–25 days increased Fusarium disease index under central European conditions in both susceptible and tolerant winter wheat cultivars, whereas increasing sowing density from 400 to 600 germinated seeds/m^2 did not show differences (Gorczyca et al. 2018). However, in cultivars that do not need vernalization, a delay in sowing dates to late autumn or early spring did not have an effect on Fusarium disease index or DON contamination (Wenda-Piesik et al. 2017).

Organic grown barley showed lower severity than conventional barley and wheat systems in Norway. However, yield was reduced around 30% (Bernhoft et al. 2012). Similarly, in Switzerland, organic systems showed lower mycotoxin accumulation levels in barley, although the number of experimental units was low (Schöneberg et al. 2016). To conclude, agricultural practices, especially crop rotations, are the first and best tool to control FHB in cereals. They have an effect on FHB levels in two ways: by reducing pathogen inoculum pressure from debris and by modifying microclimate within the plot to decrease infection.

8.2 Fungicides

Fungicide use is common in intensive cereal cropping systems. In the case of *Fusarium* diseases, demethylation inhibitors (DMIs) such as propiconazole, prothioconazole, tebuconazole or combinations of these are often used at the early or mid-anthesis stage (Freije and Wise 2015). They can reduce infection and mycotoxin contamination after a single application, but their efficacy is usually lower than 50% (Lehoczki-Krsjak et al. 2015; Paul et al. 2008). Other fungicide groups such as quinone inhibitors, succinate dehydrogenase inhibitors and DMI molecules have very low efficacy, even to increase mycotoxin production (Marques et al. 2017; Wegulo et al. 2015; Zhang et al. 2009).

AQ: 'have very low efficacy or evento increase mycotoxin production' seems unclear; please revise.

Many argue that fungicide efficacy is low due to technical gaps in the application that prevent fungicides to act in the right time and place. Indeed, *Fusarium* control efficacy depends significantly on the right timing, spray coverage and weather conditions during application (Lehoczki-Krsjak et al. 2015). Moreover, it has been shown that optimal fungicide spray timing for FHB reduction and low DON accumulation might not be the same (Yoshida et al. 2012). In barley, optimal time of application has been estimated to be 3 days after anthesis (Janssen et al. 2018) and double application of metconazole did not increase control rates (Tateishi et al. 2014). Interestingly, aerial irrigation simulating rain

at different time points after fungicide application did not lead to statistically significant increases in Fusarium disease index or mycotoxins levels (Andersen et al. 2014). On the other hand, some triazole-based fungicides applied as seed treatments have given up to 50% reduction in FCR severity, but their action is limited in time (Moya-Elizondo and Jacobsen 2016).

Excessive use of fungicides will inevitably favour the development of fungicide-resistant strains of *Fusarium*. Fungicide resistance is especially important in FHB due to the limited number of effective active ingredients (Lucas et al. 2015). Natural resistance to fungicides in wild *Fusarium* populations has been documented in China (Chen and Zhou 2009), Europe and the USA (Dubos et al. 2013). Recently, a *F. graminearum* isolate was reported to be significantly less sensitive to tebuconazole, while being highly aggressive and toxigenic (Spolti et al. 2014). Moreover, multiple genes encoding for a 14 α-demethylase (*CYP51*) have been described in *Fusarium* spp. (Yin et al. 2009). This enzyme has been associated with reduced sensitivity to azole fungicides since they are involved in the synthesis of ergosterol (Fan et al. 2013). Remarkably, some genes that are required for pathogenicity such as ABC transporters (detoxification of plant response molecules) were also upregulated during azole treatments and have been proposed as a factor contributing to fungicide resistance (Ammar et al. 2013). So, although fungicides are widely used for *Fusarium* control, their efficiency remains low. Additionally, due to the low number of effective fungicides against *Fusarium* spp., monitoring resistance emergence and understanding its mechanisms are of primary importance in reducing FHB losses.

8.3 Biological control

The use of biological control has experienced increased interest in the past years. The latent risk of fungicide resistance and the environmental concerns over the use of fungicides have become priorities for farmers and consumers. Biological control can replace or complement current measures in integrated disease management plans (Jensen et al. 2016). This approach is also attractive since it has the potential for use during grain development when the use of fungicides is ineffective, undesirable and directly prohibited. Use of biocontrol in *Fusarium*–cereal interactions has been studied extensively in recent years and reviewed by Legrand et al. (2017).

Several biological control agents have been described to provide good results for both FHB and FCR. Among the most interesting agents is *Clonostachys rosea*, due to its validated results in the field. *C. rosea* strain ACM941, when sprayed to the spikes during anthesis, can reduce disease severity and the number of *Fusarium*-damaged kernels to the same levels of tebuconazole-treated plants (Xue et al. 2014). Similarly, *C. rosea* IK726 has been shown to reduce FCR caused by *F. culmorum* in field-grown wheat and barley (Jensen et al. 2000) and to act synergistically with other biocontrol organisms against insects (Keyser et al. 2016). Furthermore, *C. rosea* IK726 can degrade the *Fusarium* mycotoxin ZEA, which partly explains its biocontrol capacity against FCR (Kosawang et al. 2014).

Similarly, treatment with the root endophytic fungi *Serendipta* (formerly *Piriformospora*) *indica* has been shown to reduce FCR symptoms under greenhouse conditions and to decrease FHB incidence and severity up to 70% in wheat when inoculated in the soil at the time of sowing (Rabiey and Shaw 2016; Rabiey et al. 2015). *S. indica* has been shown to protect roots from necrotization by reducing antioxidant enzyme activity (Harrach

et al. 2013). Likewise, bacterial strains such as *Bacillus amyloliquefaciens* FLN13 and *Lactobacillus plantarum* SLG17 have reduced Fusarium disease index up to 50% when inoculated simultaneously at flowering (Baffoni et al. 2015). *B. megaterium* BM1 showed similar results in South America (Pan et al. 2015). Also, *Pseudomonas fluorescens* LY1-8 showed reduced FCR and FHB severity by half in field trials when sprayed at flowering (Wang et al. 2015). Biocontrol agents can also be applied to crop debris to reduce inoculum pressure. Interestingly, *Streptomyces* sp. RC 87B reduced both FHB severity and DON concentrations when used in a dual application on crop debris before sowing and to the head during anthesis (Palazzini et al. 2017).

Nevertheless, only few patents have been registered (*C. rosea* ACM941 and *Bacillus* sp. TrigoCor). Likewise, only two products are available on the market; Polyversum® based on *Pythium oligandrum* with exclusive use in France (Legrand et al. 2017) and Cerall® based on *Pseudomonas chlororaphis* as a seed treatment against FCR. Despite promising initial results, most potential biological control agents sprayed to the head or coated onto the seeds lack consistency in the field, or have limited industrial properties.

9 Future trends

New genomic tools have allowed faster genotyping and made genetic marker generation more efficient. QTL mapping has moved forward at the same speed and now marker-assisted selection using single-nucleotide polymorphisms is the norm in breeding programmes. However, gene validation for hundreds of QTLs remains one of the challenges for future breeders (Jia et al. 2017). Using high-throughput technologies, transcriptome and proteome analysis can help to close this gap in the strategy termed association mapping (Collinge 2018). Similarly, the use of new gene editing techniques such as CRISPR/Cas9 could bring new tools to the table (Collinge 2018). Theoretically, breeders could aim to inactivate or modify genes in the host that are targeted by fungal effectors and therefore reduce infection or generate genetic variation by specific mutations (Jung et al. 2017).

The transgenic technology Host-Induced Gene Silencing (HIGS) has given promising results for control of *F. graminearum* in barley by silencing key fungal genes such as *CYP51* using the host molecular machinery (Koch et al. 2013). Furthermore, its non-transgenic derivative Spray-Induced Gene Silencing (SIGS) has shown that external application of these long noncoding dsRNA reduced fungal growth in directly sprayed tissue as well as non-sprayed detached leaves (Koch et al. 2016). These pathogen-tailored methods are highly specific and could represent a new window in plant protection and food safety (Majumdar et al. 2017). Regardless of current limitations on the commercial use of transgenic crops, several genes have been validated in their capacity to confer resistance and their results should not be discarded (Collinge et al. 2016). New sources of resistance could come from macroscopic phenotypic features such as floret trichomes, thicker cuticular wax to more fundamental features, such as focus on core genes that regulate primary metabolism and the production of polyamide compounds during pathogen attacks.

The 'omics' era has helped us to identify specific genes and proteins that are involved in the molecular cross-talk between pathogen and host. This can be used to fine-tune the mechanisms of action of new fungicides, given the low number of active ingredients that can be used to prevent *Fusarium* diseases. New fungicide molecules should aim to interrupt initial infection by attacking primary metabolism in the pathogen and to prevent DON production in order to restrict its role in plant response suppression. They should

also have translaminar movement and reach the apoplast, since it is where *Fusarium* hyphae colonize primarily. However, development of fungicide molecules with new modes of action is rare and enormous investments are required together with a thorough understanding of the biology of the pathogens in order to achieve success in this field. Additionally, spray technical parameters like nozzle type, drop size, angle of application, coadjutants and so forth must be optimized for existing fungicides, since their delivery needs to be optimized to achieve high efficacy.

The full deployment of biological control alternatives is currently limited by a low reliability in the field. The classical method of isolation-confrontation (dual-culture assays) is insufficient to provide information for selection of agents that are expected to replace chemical solutions. *In planta* assays are more laborious, but refine the screening process by recreating real disease scenarios. Additionally, these screening processes must include industrial-scale production parameters such as mass production, shelf life, formulation, environmental risks and so forth in their selection (Collinge et al. 2018). In order to reduce problems in low establishment, potential organisms should be isolated directly from the conditions where they are expected to be used. In the same way, assessment of their compatibility with fungicides would open a window for integrated pest management strategies for combination of modes of action and would promote low-dose fungicide use.

We should conceive the occurrence of FHB and FCR as an exception in the ecological dynamics between cereal and its microbiome (plant-associated microbial communities). This balance can be modified by the pathogen causing disease, but can also be modified by humans through agronomic practices (i.e. crop rotation, tillage, cultivar, fungicides, etc.). It should be possible to modify this equilibrium in our favour by altering the composition and structure of the microbial community, to favour beneficial organisms to the detriment of pathogens. This concept has been recurrent in the past few years as a new framework in biological control strategies (Busby et al. 2017). New biocontrol alternatives must aim to modify the microbiome composition in order to achieve greater field consistency.

Finally, without any doubt, crop rotation is the single most effective strategy in reducing cereal diseases caused *by Fusarium* spp. This and other agricultural practices are mentioned as the base of integrated pest management strategies to prevent disease and have been recommended largely by the EU (Barzman et al. 2015) (Fig. 1). These potential advances will not solve the *Fusarium* problem, but rather enrich our set of tools to complement agricultural practices in order to achieve an integrated disease management. The right combination of tools is the one that provides the disease control levels that each market requires while minimizing the environmental impacts of production. This will permit cereal production systems to adapt to new world tendencies of sustainable intensification, where environmentally friendly and consumer-based management approaches allow revenues to farmers.

10 Conclusion

Wheat and barley production is fundamental for the world economy. Constant improvement in production in a world with higher environmental standards is the challenge of contemporary agriculture and food professionals. FHB is a worldwide problem and its devastating effects have been recognized and studied for more than a century. Here, we have reviewed the current knowledge of the mechanisms involved in the interaction, its dynamics and its management methods. Currently, control of *Fusarium* diseases in

cereals is far from flawless. However, recent scientific findings suggest that control of *Fusarium* diseases in cereal crops must be built over the base of agricultural practices, crop rotations being the most important, and three main complementary pillars: increased genetic resistance, novel fungicide molecules and consistent biocontrol applications. These measures will require significant amounts of work and scientific creativity in the coming years. However, they will allow growers to adapt to the new realities of agricultural production.

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12 Where to look for further information

Some of the most fundamental knowledge about *Fusarium* diseases and *Fusarium* mycotoxins can be found in:

- Leonard, K., & Bushnell, William R. (2003). Fusarium head blight of wheat and barley. St. Paul, Minn: APS Press.
- Desjardins, A. (2006). Fusarium mycotoxins, chemistry, genetics, and biology. St. Paul, Minn: APS Press.

A complete review of the problem in Latin American countries has been recently published in:

- Alconada Magliano, T., & Chulze, Sofia Noemi. (2013). Fusarium head blight in Latin America. Dordrecht: Springer.

The U.S. Wheat and Barley Scab Initiative (USWBSI) aims to provide effective control measures against Fusarium head blight. Their website is an excellent source for lab and field protocols, fundamental information as well as news from the field:

- www.scabusa.org

An updated database for regulations around the world can be found at:

- http://www.mycotoxins.info

The Fusarium database facilitates the identification of species using nucleotide BLAST queries online:

- http://isolate.fusariumdb.org/

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