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Pathogen profile

Fusarium culmorum: causal agent of foot and root rot and head blight on wheat

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SUMMARY

Fusarium culmorum is a ubiquitous soil-borne fungus able to cause foot and root rot and Fusarium head blight on different small-grain cereals, in particular wheat and barley. It causes significant yield and quality losses and results in contamination of the grain with mycotoxins. This review summarizes recent research activities related to *F. culmorum*, including studies into its population diversity, mycotoxin biosynthesis, mechanisms of pathogenesis and resistance, the development of diagnostic tools and preliminary genome sequence surveys. We also propose potential research areas that may expand our basic understanding of the wheat–*F. culmorum* interaction and assist in the management of the disease caused by this pathogen.

Taxonomy: *Fusarium culmorum* (W.G. Smith) Sacc. Kingdom Fungi; Phylum Ascomycota; Subphylum Pezizomycotina; Class Sordariomycetes; Subclass Hypocreomycetidae; Order Hypocreales; Family Nectriaceae; Genus *Fusarium*.

Disease symptoms: Foot and root rot (also known as Fusarium crown rot): seedling blight with death of the plant before or after emergence; brown discoloration on roots and coleoptiles of the infected seedlings; brown discoloration on subcrown internodes and on the first two/three internodes of the main stem; tiller abortion; formation of whiteheads with shrivelled white grains; Fusarium head blight: prematurely bleached spikelets or blighting of the entire head, which remains empty or contains shrunken dark kernels.

Identification and detection: Morphological identification is based on the shape of the macroconidia formed on sporodochia on carnation leaf agar. The conidiophores are branched monophialides, short and wide. The macroconidia are relatively short and stout with an apical cell blunt or slightly papillate; the basal cell is foot-shaped or just notched. Macroconidia are thick-walled and curved, usually 3–5 septate, and mostly measuring 30–50 × 5.0–7.5 μm. Microconidia are absent. Oval to globose chlamydospores are formed, intercalary in the hyphae, solitary, in chains or in clumps; they are also formed from macroconidia. The colony grows very rapidly (1.6–2.2 cm/day) on potato dextrose agar (PDA) at the optimum temperature of 25 °C. The mycelium on PDA is floccose, whitish, light yellow or red. The pigment on the reverse plate on PDA varies from greyish-rose, carmine red or burgundy. A wide array of polymerase chain reaction (PCR) and real-time PCR tools, as well as complementary methods, which are summarised in the first two tables, have been developed for the detection and/or quantification of *F. culmorum* in culture and in naturally infected plant tissue.

Host range: *Fusarium culmorum* has a wide range of host plants, mainly cereals, such as wheat, barley, oats, rye, corn, sorghum and various grasses. In addition, it has been isolated from sugar beet, flax, carnation, bean, pea, asparagus, red clover, hop, leeks, Norway spruce, strawberry and potato tuber. *Fusarium culmorum* has also been associated with dermatitis on marram grass planters in the Netherlands, although its role as a causal agent of skin lesions appears questionable. It is also isolated as a symbiont able to confer resistance to abiotic stress, and has been proposed as a potential biocontrol agent to control the aquatic weed *Hydrilla* spp.

Useful websites: http://isolate.fusariumdb.org/; http://sppadbase.ipp.cnr.it/; http://www.broad.mit.edu/annotation/genome/fusarium_group/MultiHome.html; http://www.fgsc.net/Fusarium/fushome.htm; http://plantpath.psu.edu/facilities/fusarium-research-center; http://www.phi-base.org/; http://www.uniprot.org/; http://www.cabi.org/; http://www.indexfungorum.org/

INTRODUCTION

Fusarium culmorum (W.G. Smith) Sacc. is a ubiquitous soil-borne fungus with a highly competitive saprophytic capability. As a facultative parasite, it is able to cause foot and root rot (FRR) and Fusarium head blight (FHB) on different small-grain cereals, in particular wheat and barley. *Fusarium culmorum* is also known as

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a post-harvest pathogen, especially on freshly harvested grain that has not been dried or stored properly (Aldred and Magan, 2004; Eifler *et al*., 2011; Lowe *et al*., 2012; Magan *et al*., 2003, 2010). Together with *F. graminearum* Schwabe (teleomorph *Gibberella zeae*) and *F. pseudograminearum* O'Donnell and Aoki (teleomorph *Gibberella coronicola*), *F. culmorum* has been reported as one of the main pathogens of wheat worldwide (Burgess *et al*., 2001; Goswami and Kistler, 2004; Hogg *et al*., 2010; Kosiak *et al*., 2003; Miedaner *et al*., 2008; Treikale *et al*., 2010; Wagacha and Muthomi, 2007; Wang *et al*., 2006).

Yield and quality losses are particularly important when *F. culmorum* induces FHB, which develops from infection at anthesis and spreads until grain harvest, causing grain contamination with mycotoxins, such as type B trichothecenes, zearalenone and fusarins (Hope *et al*., 2005; Jennings *et al*., 2004; Kammoun *et al*., 2010; Lacey *et al*., 1999; Placinta *et al*., 1999; Rohweder *et al*., 2011; Visconti and Pascale, 2010). The sesquiterpene epoxide trichothecenes are considered to be the most bioactive compounds produced by *F. culmorum*. These mycotoxins are able to inhibit eukaryotic protein synthesis (Wei and McLaughlin, 1974) and cause toxicoses in humans or animals consuming contaminated food or feed (Sudakin, 2003). They have also been reported to induce apoptosis (Desmond *et al*., 2008; Yang *et al*., 2000) and play an important role as virulence factors (Bai *et al*., 2002; Desjardins *et al*., 1996, 2000; Harris *et al*., 1999; Jansen *et al*., 2005; Maier *et al*., 2006; McCormick, 2003; Proctor *et al*., 1995, 2002; Scherm *et al*., 2011; Ward *et al*., 2008; Zhang *et al*., 2010).

The purpose of this profile is to provide an overview of the recent research activities related to *F. culmorum*, including those on population diversity, mycotoxin biosynthesis, mechanisms of pathogenesis and resistance, the development of diagnostic tools and preliminary genome sequence surveys (see Tables 1 and 2, respectively, for a list of PCR-based and non PCR-based approaches to discriminate and detect *F. culmorum*). We also propose potential research areas that may expand our basic understanding of the wheat–*F. culmorum* interaction and ultimately assist in the management of the different facies of the disease caused by this pathogen.

DISEASE SYMPTOMS

Fusarium culmorum causes two distinct diseases on wheat: FRR and FHB, also known as ear blight or scab. FRR symptoms vary depending on the time of infection: if the fungus attacks at the early stage, just after sowing, pre- and post-emergence seedling death occurs, with brown discoloration on the coleoptiles, roots and the pseudostem; if the infection starts later in the season, brown lesions appear on the first two or three internodes of the main stem and tiller abortion occurs (Fig. 1B). In the presence of high humidity, a reddish-pink discoloration is often evident on the nodes caused by the presence of sporulating mycelium (Fig. 1C). The presence of whiteheads with shrivelled grain—or no grain at all—is easily observed when the wheat is still immature (Fig. 1D,E). Infected plants are more prone to lodging. FHB symptoms include partial head blighting, with the appearance of one or more prematurely bleached spikelets, or blighting of the entire head, which is easily observed when wheat has not yet reached the ripening stage (Fig. 2A,B). Initially, infected spikelets show light-brown, water-soaked spots on the glumes, which then become dark brown. Infected spikelets remain empty or contain shrunken grey/brown kernels. Browning on the rachilla and the rachis can be observed and, under favourable conditions, the fungus may infect the stem below the head, inducing a brown/purplish discoloration (Fig. 2C). Pink to orange sporodochia may be evident at the base of the spikelets or between the glumes and lemmas, if the environmental conditions are particularly humid (Fig. 2D,F).

EPIDEMIOLOGY

Fusarium culmorum has been traditionally reported as the incitant of FHB in northern, central and western Europe (Muthomi *et al*., 2000;de Nijs *et al*., 1997; Parry *et al*., 1995). However, recently, in northern Europe, a change is being observed in the frequency of isolation, and *F. culmorum* is seldom reported compared with *F. graminearum*. This progressive switch may be explained by the widespread use of feed maize as a rotation crop with wheat in northern Europe, with consequent *F. graminearum* inoculum build-up in the soil. It is noteworthy that *F. culmorum* is occasionally isolated from maize crops and maize kernels, but never as the main pathogen (Logrieco *et al*., 2002; Scauflaire *et al*., 2011; Van Asselt *et al*., 2012). Other reasons for the transition from *F. culmorum* to *F. graminearum* may be related to the gradual adaptation of *F. graminearum* to colder climates as a result of genome plasticity (Lysøe *et al*., 2011; Raffaele and Kamoun, 2012) or to the rise in average temperatures caused by climate change (Jennings *et al*., 2004; Waalwijk *et al*., 2003; West *et al*., 2012; Xu *et al*., 2005). However, in Luxembourg, following the year 2011 with hardly any precipitation in May, 90% of the blighted spikes were infected by *F. culmorum*, whereas only 10% were infected by *F. graminearum*, suggesting a role of climatic conditions in driving the prevalence of each species, reversing drastically the previous species distribution (Giraud *et al*., 2010).

Contrary to early reports from colder areas in central and northern Europe, *F. culmorum* is now frequently reported as the main agent of FHB in the Mediterranean region, and particularly in years characterized by wet conditions during the phenological phases of flowering and kernel filling (Corazza *et al*., 2002; Fakhfakh *et al*., 2011; Kammoun *et al*., 2010; Pancaldi *et al*., 2010). The greater incidence of FHB caused by *F. culmorum* in these areas is correlated with its presence as the main cause of FRR, a disease that is particularly severe on durum wheat in southern Italy and North Africa.

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Table 1 Summary of published primers used for species and chemotype determination in *Fusarium culmorum*.

Identification of	Primers and probes (5′ → 3′)	Target DNA	PCR technique	Reference
Species (*F. culmorum* and *F. graminearum*)	**FcF** CAAAAGCTTCCCGAGTGTGTC **FcR** GGCGAAGGTTCAAGGATGAC	Unknown	Conventional PCR	Baturo-Ciesniewska and Suchorzynska (2011); Doohan *et al*. (1998)
Species (not able to distinguish from *F. cerealis*)	**FculC561fwd** CACCGTCATTGGTATGTTGTCACT **FculC614rev** CGGGAGCGTCTGATAGTCG	*ef1-α*	Real-time PCR	Nicolaisen *et al*. (2009)
Species (together with *F cerealis* and *F. graminearum*)	**FIP-hyd5** GCACAGCACTGGGAAGTGCGAGAAGCGACAGGCCTACA **BIP-hyd5** TGGGTGTTGCTGACCTCGACGGGGCTGTTCATGTTAGCT **B3-hyd4** GACAGCGCTGAAGTTGTC **LoopB-hyd5** CCGTAAGTACTCGAGTCTG **LoopF-hyd5** GTAGAGGCCACTGCAAGG **F3-hyd5** CTTGGAGCCGTTGTCTCTG	*Hyd 5*	LAMP PCR	Denschlag *et al*. (2012)
Species (together with *F. crockwellense*)	**CRO-C fwd** CTCAGTGTCCACCGCGTTGCGTAGTGT **CRO-C rev** AAGCAGGAAACAGAAACCCTTTCC	RAPD fragment	Conventional PCR	Yoder and Christianson (1998)
Species (together with *F. graminearum*)	**CUL-A fwd** TTTCAGCGGGCAACTTTGGGTAGA **CUL-A rev** AAGCTGAAATACGCGGTTGATAGG	RAPD fragment	Conventional PCR	Yoder and Christianson (1998)
Species	**C51END fwd** AACTGAATTGATCGCAAGC **C51END rev** CCCTTCTTACGCCAATCTC	Unknown	Real-time PCR	Covarelli *et al*. (2012)
Species	**OPT18F470** GATGCCAGACCAAGACGAAG **OPT18R470** GATGCCAGACGCACTAAGAT	SCAR	Conventional PCR Real-time PCR*	Baturo-Ciesniewska and Suchorzynska (2011); Brandfass and Karlovsky 2006; Schilling *et al*. (1996)
Species	**Fc92s1 forward** TTCACTAGATCGTCCGGCAG **Fc92s1 reverse** GAGCCCTCCAAGCGAGAAG	Unknown	Real-time PCR	Leisova *et al*. (2006)
Species	**Fc01F** ATGGTGAACTCGTCGTGGC **Fc01R** CCCTTCTTACGCCAATCTCG	RAPD fragment	Conventional PCR	Baturo-Ciesniewska and Suchorzynska (2011); Nicholson *et al*. (1998)
Species	**Fcg17F** TCGATATACCGTGCGATTTCC **Fcg17R** TACAGACACCGTCAGGGGG	RAPD fragment	Conventional PCR	Baturo-Ciesniewska and Suchorzynska (2011); Nicholson *et al*. (1998)
Species	**175F** TTTTAGTGGAACTTCTGAGTAT **430R** AGTGCAGCAGGACTGCAGC	ITS region	Fluorescent-labelled PCR-based assay	Mishra *et al*. (2003)
Species	**culmorum MGB-R** GAACGCTGCCCTCAAGCTT **culmorum MGB-F** TCACCCAAGACGGGAATGA **Probe** CACTTGGATATATTTCC	Genomic DNA	Real-time PCR (TaqMan)	Waalwijk *et al*. (2004)
Type B trichothecene producers	**Fcu-F** GACTATCATTATGCTTGCGAGAG **Fgc-R** CTCTCATATACCCTCCG	IGS region	Conventional PCR	Baturo-Ciesniewska and Suchorzynska (2011); Jurado *et al*. (2005)
15-ADON subchemotype	**Tri3F971** CATCATACTCGCTCTGCTG **Tri3R1679** TT(AG)TAGTTTGCATCATT(AG)TAG	*TRI3*	Conventional PCR	Pasquali *et al*. (2011); Quarta *et al*. (2006)
3-ADON subchemotype	**Tri3F1325** GCATTGGCTAACACATGA **Tri3R1679** TT(AG)TAGTTTGCATCATT(AG)TAG	*TRI3*	Conventional PCR	Pasquali *et al*. (2011); Quarta *et al*. (2006)
Nivalenol subchemotype	**Tri7F340** ATCGTGTACAAGGTTTACG **Tri7R965** TTCAAGTAACGTTCGACAAT	*TRI7*	Conventional PCR	Pasquali *et al*. (2011); Quarta *et al*. (2005)
High-deoxynivalenol-producing strains	**N1-2** CTTGTTAAGCTAAGCGTTTT **N1-2R** AACCCCTTTCCTATGTGTTA	*TRI6/TRI5* intergenic region	Conventional PCR	Bakan *et al*. (2002)
Low-deoxynivalenol-producing strains	**4056** ATCCCTCAAAAACTGCCGCT **3551** ACTTTCCCACCGAGTATTTC	*TRI6/TRI5* intergenic region	Conventional PCR	Bakan *et al*. (2002)

Table 1 Continued.

Identification of	Primers and probes (5′ → 3′)	Target DNA	PCR technique	Reference
Species (together with *F. graminearum* and *F. pseudograminearum*)	**Gzeae87T forward** CGCATCGAGAATTTGCA **Gzeae87T reverse** TGGCGAGGCTGAGCAAAG **Gzeae87T probe** 6FAM-TGCTTACAACAAGGCTGCCCACCA-TAMRA	*TRI5*	Real-time PCR (TaqMan)	Strausbaugh *et al*. (2005)
Deoxynivalenol-producing isolates (*F. graminearum* and *F. culmorum*)	**22F** AATATGGAAAACGGAGTTCATCTACA **122R** ATTGCCGGTGCCTGAAAGT	*TRI6-TRI5* intergenic region	Real-time PCR (SYBR Green I)	Terzi *et al*. (2007)
PKS13-containing strains (*F. culmorum* and *F. graminearum*)	**ZEA-F** CTGAGAAATATCGCTACACTACCGAC **ZEA-R** CCCACTCAGGTTGATTTTCGTC	*PKS13*	Conventional PCR/Real-time PCR (SYBR Green I)	Atoui *et al*. (2012)
Deoxynivalenol-producing strain	**Tri7F** TGCGTGGCAATATCTTCTTCTA **Tri7DON** GTGCTAATATTGTGCTAATATTGTGC	*TRI7*	Conventional PCR	Baturo-Ciesniewska and Suchorzynska (2011); Chandler *et al*. (2003)
Deoxynivalenol-producing strain	**Tri13F** CATCATGAGACTTGTKCRAGTTTGGGC **Tri13DONR** GCTAGATCGATTGTTGCATTGAG	*TRI13*	Conventional PCR	Baturo-Ciesniewska and Suchorzynska (2011); Chandler *et al*. (2003)
Nivalenol-producing strain	**Tri7F** TGCGTGGCAATATCTTCTTCTA **Tri7NIV** TGTGGAAGCCGCAGA	*TRI7*	Conventional PCR	Baturo-Ciesniewska and Suchorzynska (2011); Chandler *et al*. (2003)
Nivalenol-producing strain	**Tri13NIVF** CCAAATCCGAAAACCGCA **Tri13R** TTGAAAGCTCCAATGTCGTG	*TRI13*	Conventional PCR	Baturo-Ciesniewska and Suchorzynska (2011); Chandler *et al*. (2003)
3-ADON-producing strain	**Tri303F** GATGGCCGCAAGTGGA **Tri303R** GCCGGACTGCCCTATTG	*TRI3*	Conventional PCR	Baturo-Ciesniewska and Suchorzynska (2011); Jennings *et al*. (2004)
Trichothecene producer	**Tox5-1** GCTGCTCATCACTTTGCTCAG **Tox5-2** CTGATCTGGTCACGCTCATC	*TRI5*	Conventional PCR	Baturo-Ciesniewska and Suchorzynska (2011); Niessen and Vogel (1998)
Nivalenol-producing strain	**12NF** TCTCCTCGTTGTATCTGG **12CON** CATGAGCATGGTGATGTC	*TRI12*	Conventional PCR	Pasquali *et al*. (2011); Ward *et al*. (2002)
Deoxynivalenol-producing strain	**12-3F** CTTTGGCAAGCCCGTGCA **12CON** CATGAGCATGGTGATGTC	*TRI12*	Conventional PCR	Pasquali *et al*. (2011); Ward *et al*. (2002)
Nivalenol-producing strain	**Tri13P1** CTCSACCGCATCGAAGASTCTC **Tri13P2** GAASGTCGCARGACCTTGTTTC	*TRI13*	Conventional PCR	Pasquali *et al*. (2011); Wang *et al*. (2008)
3-ADON-producing strains	**3ADONf** AACATGATCGGTGAGGTATCGA **3ADONr** CCATGGCGCTGGGAGTT	*TRI12*	Real-time PCR	Nielsen *et al*. (2012)
Nivalenol-producing strain	**NIVf** GCCCATATTCGCGACAATGT **NIVr** GGCGAACTGATGAGTAACAAAACC	*TRI12*	Real-time PCR	Nielsen *et al*. (2012)
3-ADON-producing strains (*F. culmorum* and *F. graminearum*)	**3ADON fwd** CATGCGGGACTTTGATCGAT **3ADON rev** TTTGTCCGCTTTCTTTCTATCATAAA **3ADON probe** FAM-CTCACCGATCATGTTC-MGB	*TRI12*	Taqman real-time PCR	Kulik (2011)
Nivalenol-producing strain (*F. culmorum* and *F. graminearum*)	**NIV fwd** TCGCCAGTCTCTGCATGAAG **NIV rev** CCTTATCCGCTTTCTTTCTATCATAAA **NIV probe** FAM-CTGATCATGTCCCGCATC-MGB	*TRI12*	Taqman real-time PCR	Kulik (2011)
Zearalenone producer	**PKS4-PS.1** GTGGGCTTCGCTAGACCGTGAGTT **PKS4-PS.2** ATGCCCTGATGAAGAGTTTGA	*PKS4*	Real-time PCR	Baturo-Ciesniewska and Suchorzynska (2011); Lysøe *et al*. (2006)
Zearalenone producer	**F1** CGTCTTCGAGAAGATGACAT **R1** TGTTCTGCAAGCACTCCGA	*PKS4*	PCR	Baturo-Ciesniewska and Suchorzynska (2011); Meng *et al*. (2010)

ADON, acetylated deoxynivalenol; PCR, polymerase chain reaction; RAPD, random amplification of polymorphic DNA; SCAR, sequence characterized amplified region.

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Table 2 Non-polymerase chain reaction (PCR)-based approaches to discriminate and detect *Fusarium culmorum*.

Technology employed	Reference
Surface plasmon resonance (SPR) sensor based on DNA hybridization	Zezza *et al*. (2006)
Luminex assay to discriminate *Fusarium* species and chemotypes	Ward *et al*. (2008)
DNA microarray for detection and identification of 14 *Fusarium* species	Kristensen *et al*. (2007)
Spore shape discrimination analysed by computerized algorithms	Dubos *et al*. (2012)
Metabolomic analysis and monitoring of the metabolic activity	Lowe *et al*. (2010)
Electronic nose for discriminating species infecting grains	Eifler *et al*. (2011)
Quick matrix-assisted laser desorption/ionization (MALDI) linear time-of-flight mass spectrometry analysis of fungal spores	Kemptner *et al*. (2009)

Key factors in the development of FRR are the previous crop, residue management, nitrogen fertilization, plant density and the environmental conditions. Conidial germination and germ tube extension on sterile and unsterile wheat straw leaf sheaths were significantly higher relative to other crop residue colonizers, such as *Gliocladium*, *Trichoderma* and *Penicillium* spp., when tested at different water potential × temperature (Magan, 1988). Therefore, wheat monoculture and/or rotation with another cereal crop (such as barley, triticale, rye, spelt, oat or corn) boosts the inoculum and, consequently, the chances of increasing FRR severity: although cereals are not equally sensitive to *F. culmorum*, all may contribute to maintain inoculum survival in the soil. High nitrogen fertilization rates and high sowing density are believed to increase the incidence of FRR: increased leaf index and transpiration rates and the reduction of plant water potential induce water stress and, consequently, a higher sensitivity to the pathogen (Davis *et al*., 2009; Papendick and Cook, 1974).

FRR by *F. culmorum* is severe when wheat is grown in warm areas, where the host plant is more subject to water stress (Bateman, 1993; Cariddi and Catalano, 1990; Chekali *et al*., 2010; Colhoun *et al*., 1968; Inglis and Cook, 1986; Papendick and Cook, 1974; Parry, 1990; Prew *et al*., 1995). Drought conditions increase the susceptibility of the plant rather than the virulence of the fungus. However, FHB occurs preferentially when the pathogen is present at the soil level, and the weather is moist and warm, with frequent rains between flowering and kernel filling stages (Bateman, 2005). Rain is an essential determinant of FHB infection, as demonstrated experimentally on wheat crops receiving overhead irrigation (Strausbaugh and Maloy, 1986). The macroconidia that are found in soil on crop residues reach the ear by rain splash, wind or insects, attaining distances of up to 60 cm vertically and 1 m horizontally (Jenkinson and Parry, 1994; Parry *et al*., 1995; Rossi *et al*., 2002). Compared with *F. graminearum*, *F. culmorum* does not produce ascospores, being unable to differentiate sexual perithecia. From an epidemiological standpoint, this is paramount, given the crucial role of wind-borne ascospores in the spread of FHB caused by the former species (Markell and Francl, 2003).

Once the inoculum reaches the ear, humidity and temperature in the crop microclimate play a critical role: it takes at least 24 h of moisture with temperatures above 15 °C, with an optimum of 25 °C, to allow infection (Doohan *et al*., 2003; Parry *et al*., 1995). Nonetheless, among the species causing FHB, *F. culmorum* has the smallest need for the presence of high relative humidity to infect wheat (Klix *et al*., 2008; Rossi *et al*., 2001).

POPULATION DIVERSITY AND MYCOTOXIN PRODUCTION

The perfect stage (teleomorph) of *F. culmorum* is not known, even though transcribed mating type genes have been identified in this species. Only one MAT idiomorph (MAT1-1 or MAT1-2) has been reported so far, postulating heterothallism (Kerényi *et al*., 2004; Mishra *et al*., 2003; Obanor *et al*., 2010; Tòth *et al*., 2004). It is noteworthy that, among a vast majority of isolates from Turkey carrying either the MAT-1 or MAT-2 sequence, Çepni *et al*. (2012) were recently able to identify two *F. culmorum* isolates that carried both sequences.

The genetic variability of *F. culmorum* in different geographical areas suggests that genetic exchange occurs or has occurred in the past, as the population structure is not clonal (Miedaner *et al*., 2001; Mishra *et al*., 2003; Tòth *et al*., 2004).

Population studies carried out within restricted geographical areas, or even at the single field level, have reported a wide genetic variability, whereas relatively modest differences have been detected among populations obtained from different climatic regions (Gargouri *et al*., 2003; Nicholson *et al*., 1993). A high level of diversity has also been found recently in *F. culmorum* isolates from Turkey by intergenic spacer-restriction fragment length polymorphism (IGS-RFLP) analysis, further confirming the wide genetic variability associated with FRR disease (Çepni *et al*., 2012). A phylogenetic study conducted with over 100 isolates of *F. culmorum* from Australia, West Asia, North Africa and Europe identified three to four distinct groups or lineages. However, no correlation was found between lineages and their geographical origin, with the exception of one cluster including isolates from a single area (Obanor *et al*., 2010).

Two chemotypes have been described in *F. culmorum*: chemotype I, which produces deoxynivalenol (DON) and/or its acetylated derivatives (3-ADON, 15-ADON), and chemotype II, which produces nivalenol (NIV) and/or fusarenone-X (FUS), NIV being 10 times more toxic than DON (Minervini *et al*., 2004). DNA sequence variation in the coding region of the trichothecene biosynthetic gene *TRI8* was found in *Fusarium* spp., including *F. culmorum*, indicating that differential activity of the Tri8 protein (i.e. deacetylation of the trichothecene biosynthetic intermediate 3,15-

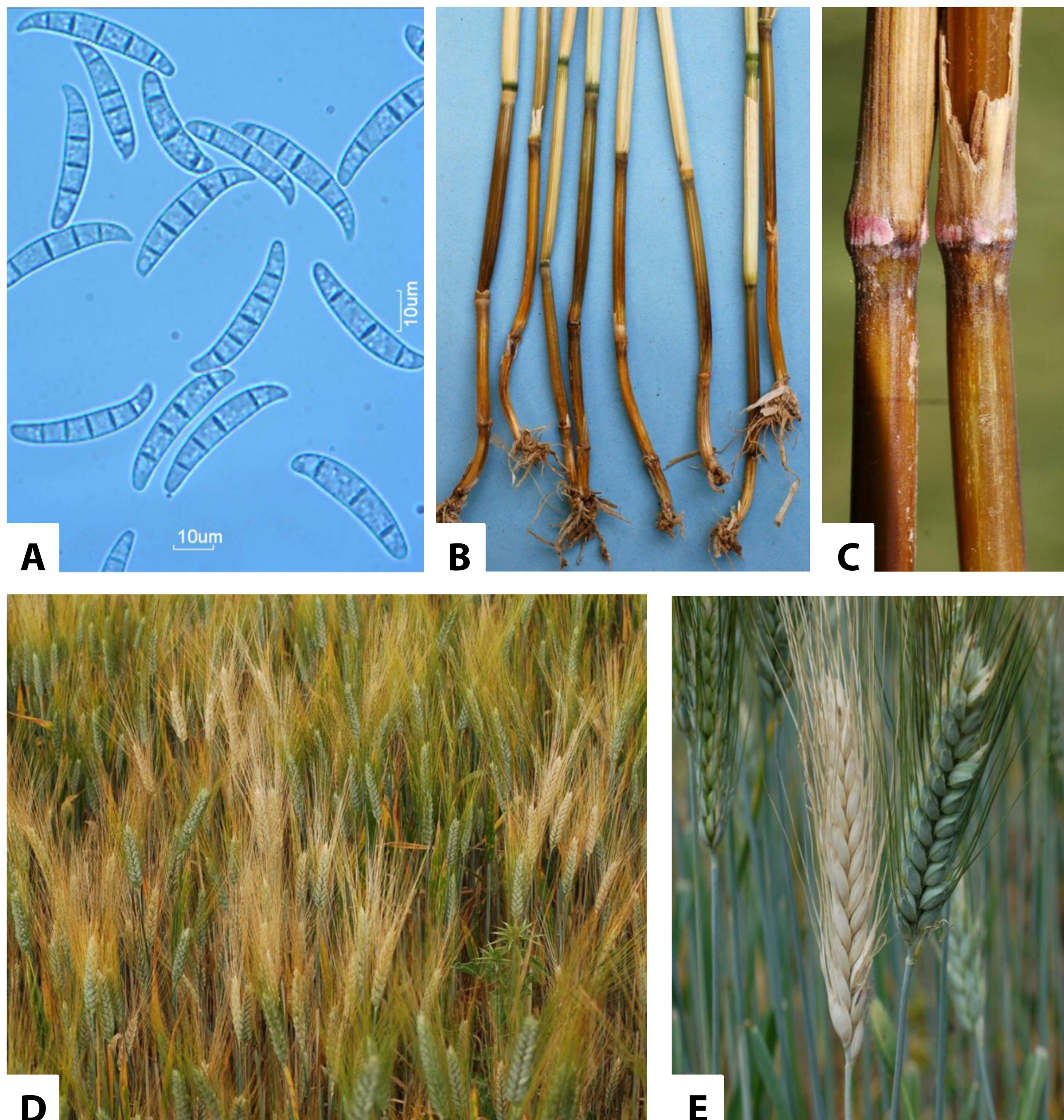

Fig. 1 Foot and root rot (FRR) symptoms: (A) macroconidia; (B) browning on the stem base; (C) reddish-pink discoloration on the basal nodes; (D,E) presence of whiteheads.

diacetyldeoxynivalenol at carbon 15 versus carbon 3 to yield 3-ADON or 15-ADON, respectively) determines the 3-ADON and 15-ADON subchemotypes in *Fusarium* (Alexander *et al*., 2011).

Studies on *F. culmorum* chemotypes are less frequent than those focusing on *F. graminearum*, but it is possible to trace their distribution in some geographical areas (Table 3).

The link between the presence of the pathogen and its toxins (in this case, type B trichothecenes) is often complicated by the complexity of toxin induction and pathogen adaptation. Although *F. culmorum* has been reported to be one of the main fungal species associated with diseased wheat in warmer regions, such as Turkey (Tunalı *et al*., 2006), Tunisia (Kammoun *et al*., 2010),

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Fig. 2 Fusarium head blight (FHB) symptoms: (A,B) head blight symptoms; (C) brown/purplish discoloration below head; (D–F) orange sporodochia on spikelets.

Australia and New Zealand (Lauren *et al*., 1992), no clear data on its role in toxin accumulation are evident. Moreover, although this species was the most prevalent in 2009 in the central region of Poland, the level of toxin contamination reported in the grains was very low, and no direct correlation between fungal contamination and toxin accumulation could be found (Chelkowski *et al*., 2012). The identification of the chemotype may provide insight into the toxigenic potential of *F. culmorum* isolates. For example, the presence of *F. culmorum* with the NIV subchemotype has been linked to the accumulation of NIV in wheat harvested in Luxembourg during 2007 and 2008 (Pasquali *et al*., 2010), confirming the findings obtained in a within-field comparison experiment described by Xu *et al*. (2008). Similar results pinpointing a role of *F. culmorum* in the accumulation of NIV have been reported in a recent

Table 3 Distribution of *Fusarium culmorum* chemotypes: country, chemotyping method used, number of isolates analysed, main finding and bibliographic reference.

Country	Chemotyping method used	Number of isolates analysed	Main finding	Reference
Europe	Chemical	42	~84% DON producers, ~16% NIV producers	Gang *et al*. (1998)
Germany	Chemical	27	~60% NIV producers, ~40% DON producers	Muthomi *et al*. (2000)
Norway	Chemical	23	Mostly 3-ADON producers, two NIV producers	Langseth *et al*. (2001)
France	Genetic and chemical	60	58% NIV producers, 42% DON producers	Bakan *et al*. (2001, 2002)
Denmark, Germany, Austria	Chemical	102	1995 sampling: ~90% DON producers, ~10% NIV producers	Hestbjerg *et al*. (2002)
The Netherlands	Genetic	85	2000–2001 sampling: mostly NIV producers	Waalwijk *et al*. (2003)
Worldwide (Australia, Canada, Israel, Hungary, Germany, Denmark, the Netherlands, Morocco)	Genetic and chemical	37	19% NIV producers, 81% 3-ADON producers	Tòth *et al*. (2004)
UK	Genetic	157	DON producers are prevalent, but NIV producers are distributed consistently	Jennings *et al*. (2004)
Europe (Spain, Italy, Poland, Norway, the Netherlands, France, Finland, former Yugoslavia)	Genetic	55	~20% NIV producers, ~80% 3-ADON producers	Quarta *et al*. (2005)
Belgium	Genetic	128	In 2007 (95%) and in 2008 (88%) NIV producers are the most diffused	Audenaert *et al*. (2009)
Luxembourg	Genetic and chemical	175	3-ADON and NIV producers are evenly distributed Chemotyping is useful to predict toxin content Chemical analysis confirms genetic chemotyping	Pasquali *et al*. (2010)
Tunisia	Genetic and chemical	100	Mostly 3-ADON producers, 2% NIV producers Chemical analysis confirms genetic chemotyping	Kammoun *et al*. (2010)
Poland	Genetic	68	6% NIV producers, 94% 3-ADON producers	Baturo-Ciesniewska and Suchorzynska (2011)
Turkey	Genetic	21	100% 3-ADON producers	Yörük and Albayrak (2012)

ADON, acetylated deoxynivalenol; DON, deoxynivalenol; NIV, nivalenol.

screening of historical Danish seed samples by real-time PCR (Nielsen *et al*., 2012).

HOST–PATHOGEN INTERACTION

Although a wide array of information on *F. culmorum* pathogenesis can be inferred from reports using *F. graminearum* as the species of interest, in the present review, we have attempted to limit references to related *Fusarium* species only when absolutely necessary. *Fusarium culmorum* remains viable as mycelium in crop residues left on the ground surface, and can survive in soil for 2–4 years by forming chlamydospores (Bateman *et al*., 1998; Cook, 1980; Inglis and Cook, 1986). When the seed germinates, the fungus penetrates through the lesions that are formed during primary root emergence, and then progresses towards the culm. Alternatively, it penetrates through the stomata at the insertion point of the basal leaf sheath towards the stem. The colonization follows, initially, an intercellular apoplastic pathway between cells of the epidermis and cortex; subsequently, the fungus progresses intracellularly in the symplast to complete colonization of the tissues (Beccari *et al*., 2011; Covarelli *et al*., 2012; Pettitt and Parry, 2001). The fungus may then grow further along the stem, although it is usually limited to the first basal internodes. The symptoms of basal browning may occur prior to the presence of the fungus in these portions, as a result of the plant response to infection (Beccari *et al*., 2011; Covarelli *et al*., 2012).

FHB infection occurs between flowering and the soft dough stage (GS 65–85; Zadoks' scale modified by Tottman and Makepeace, 1979), the phases between flowering and the milk stage (GS 65–77) being the most favourable for the infection by *F. culmorum* (Lacey *et al*., 1999). Once the macroconidia arrive onto the ear, they germinate rapidly and the fungus penetrates into host tissues, either directly through the stomata, or through the floret mouth or crevices formed between the palea and lemma, and then progresses inter- and intracellularly and reaches the endosperm within 12–24 h. Betaine and choline, which are contained in the anthers, stimulate the growth of conidial germ tubes towards the head surface (Strange *et al*., 1974, 1978). Similar to other FHB pathogens, *F. culmorum* may have an initial brief biotrophic phase within plant tissues, but then shifts to a necrotrophic stage through the production of trichothecenes and cell wall-degrading enzymes (CWDEs; Bushnell *et al*., 2003).

The infection process by *F. culmorum* is strongly influenced by temperature, humidity, carbon and nitrogen availability, as well as the ability of the specific strain to produce mycotoxins that may confer a higher aggressiveness by inhibiting the defence response

by the plant. Key factors for its growth are temperature and water availability (water activity a_w; Magan *et al*., 2006). Schmidt-Heydt *et al*. (2011) compared the effect of $a_w \times$ temperature of one isolate of *F. culmorum* and *F. graminearum* on growth, *F. culmorum* showing an optimum at 30 °C and 0.98a_w, whereas its minimum limit for growth was 15 °C over 0.88–0.995a_w. Germination of *F. culmorum* macroconidia is restricted to a minimum of 0.86a_w, but is functional over a wide temperature range from 5 to 35 °C (Magan *et al*., 2006). *Fusarium culmorum* hydrolytic enzymes are produced over the same broad temperature range, allowing the rapid utilization of nutritional resources (Magan and Lynch, 1986).

Mycotoxin biosynthesis is mainly influenced by temperature and moisture (Homdork *et al*., 2000; Tanaka *et al*., 1988). Studies with *F. culmorum* and *F. graminearum* isolates from Spain (Llorens *et al*., 2004) showed that both fungi require high humidity (>0.90a_w) to support trichothecene production, with optimum temperatures of 25–28 °C for DON, 20 °C for NIV and a minimum of 15 °C for 3-ADON. *Fusarium culmorum* demonstrated a significantly higher mycotoxigenic rate (up to five times higher for type B trichothecenes) than *F. graminearum*, and the toxin biosynthesis could not be correlated with mycelial growth (Llorens *et al*., 2004; Lori *et al*., 1999).

Trichothecene production, which is driven by the expression of the *TRI5* gene encoding the key biosynthesis enzyme trichodiene synthase, can be observed as early as 36 h post-inoculation during the colonization of wheat spikelets (Beccari *et al*., 2011; Kang and Buchenauer, 2002). The ability of aggressive strains of *F. culmorum* to infect wheat is related to their ability to produce larger amounts of DON in culture or in infected tissues (Hestbjerg *et al*., 2002; Manka *et al*., 1985; Scherm *et al*., 2011), although correlation is not always linear (Gang *et al*., 1998). Similar to *F. graminearum*, trichothecene mycotoxins produced by *F. culmorum* are essential for the spread of the disease by inhibiting defence mechanisms activated by the plant (Wagacha and Muthomi, 2007). Following inoculation of the stem base of soft wheat seedlings with *F. culmorum*, Covarelli *et al*. (2012) demonstrated the translocation of DON to the head, even though the fungus was unable to grow systemically beyond the third node. This finding suggests that FRR may represent an additional potential source of grain contamination, providing an explanation for previous reports on the presence of DON in grain harvested in the field, even in the absence of detectable fungus (Xu *et al*., 2008).

Different plant compounds involved in host–pathogen interactions are able to interfere with mycotoxin production within plant tissue (Boutigny *et al*., 2008). On infection, plant cells respond with a hypersensitive reaction by the generation of reactive oxygen species (ROS), such as H_2O_2 and superoxide. The strong oxidative properties of H_2O_2 modulate trichothecene biosynthesis (Ponts *et al*., 2006; Sweeney and Dobson, 1999), leading to increased expression of *TRI* genes (Ochiai *et al*., 2007; Ponts *et al*., 2007). *In vitro* production of DON and ADON by *F. culmorum* chemotype I isolates was enhanced after H_2O_2 treatment, whereas NIV and FUS production by chemotype II isolates was reduced (Ponts *et al*., 2009). Differences in the efficiencies of detoxification have been described in *F. culmorum* isolates of the two chemotypes. Usually, chemotype I isolates exposed to oxidative stress react with an increase in catalase activity, resulting in a higher H_2O_2-destroying capacity (Ponts *et al*., 2009).

Typical growth patterns of *F. culmorum* are accompanied by a pH increase during infection (Lamour and Marchant, 1977), followed by increased extracellular enzyme expression activity and DON production. The role of CWDEs as virulence factors in *F. culmorum* has been investigated extensively (Cooper *et al*., 1988; Hestbjerg *et al*., 2002; Miedaner *et al*., 1997; Tunalı *et al*., 2012; Wang *et al*., 2006). The production of CWDEs able to hydrolyse cellulose, xylan and pectin of the plant cell wall (PCW) allows *F. culmorum* to invade host tissues within 3–4 days (Kang and Buchenauer, 2002). These alterations may occur even before the presence of fungal hyphae within the host tissues, suggesting an apoplastic movement of these enzymes (Kang and Buchenauer, 2000a, 2000b).

Fusarium culmorum creates the conditions for maximum activity of its pectin lyases (PNLs) and other depolymerizing enzymes by raising the apoplastic pH from 6 to 7.3. When grown with pectin as the sole carbon source, *F. culmorum* modulates the pH to more alkaline conditions, favouring significantly PNL production and repressing polygalacturonase (PG) expression, which has an activity window at the very initial stages of infection. This pH change triggers the synthesis of additional 'weapons', such as subtilisin and trypsin-like enzymes, which are relevant in this colonization phase (Aleandri *et al*., 2007; Pekkarinen and Jones, 2002; Pekkarinen *et al*., 2002). *In vivo*, *F. culmorum* attacks an arabinoxylan-rich cell wall (constituting up to 40% of its components) of graminaceous crops, and produces much more xylanases than other pathogens (Bëlien *et al*., 2006; Carpita, 1996; Hatsch *et al*., 2006). Moreover, effective hydrolysis of PCW requires the synergistic action of several CWDEs that have been found to be expressed and to act in complexes (Alfonso *et al*., 1995; Collins *et al*., 2005; Jaroszuk-Scisel *et al*., 2011). The activities of seven CWDEs (glucanases, chitinases, xylanases, endo- and exocellulases, pectinases, PGs) have been traced in cultures of *F. culmorum* grown on fungal cell walls (FCWs) or PCW as carbon source, with glucanases, chitinases, xylanases and pectinases revealing a significantly higher activity. Replacement of FCW by PCW triggers an increase in PG activity, underlining their role in the initial phase of host cell wall attack (Jaroszuk-Scisel and Kurek, 2012). *Fusarium culmorum* cultures with FCW as the only carbon source enhance their acid glucanase and chitinase repertoire, whereas PCW-based cultures produce high concentrations of xylanases, as also documented for *Fusarium*-infected barley (Jaroszuk-Scisel and Kurek, 2012; Schwarz *et al*., 2002). Differences in the disease induction

and tissue colonization between pathogenic and nonpathogenic isolates of *F. culmorum* have also been related to their different CWDE efficiencies (Jaroszuk-Scisel and Kurek, 2012) and to their ability to induce local and systemic defence responses, i.e. cell wall thickening or oxidative burst (Jaroszuk-Scisel *et al*., 2008; Martinez *et al*., 2000).

On infection with an *F. culmorum* spore suspension, wheat seeds and seedlings express several pathogenesis-related (PR) proteins, including glucanases (PR1, PR2), chitinase (PR3), peroxidase (POX) and the PR protein Wheatwin1-2 (PR4) (Aleandri *et al*., 2008; Bertini *et al*., 2003; Caruso *et al*., 1999). In *in vitro* experiments, stimulation of wheat seeds with different chemical inducers, such as salicylic acid (SA) and jasmonic acid (JA), or by mechanical damage through wounding, was followed in each case by an increase in PR4 expression, indicating its regulation by these pathways (Bertini *et al*., 2003). *Fusarium culmorum*-infected wheat roots, instead, underwent increased expression of defence-associated genes in leaf sheaths which had not yet been in contact with the fungus, indicating the role of a systemic response in FRR (Beccari *et al*., 2011).

Effective and persistent resistance in the host plant can be induced by low-molecular-mass molecules able to restrict fungal growth in the different tissue layers or by the inhibition of fungal CWDEs. In wheat, xylanase-specific inhibitors, such as TAXI (Goesaert *et al*., 2003), XIP (Juge *et al*., 2004), thaumatin-like XI (TLXI; Fierens *et al*., 2007) and PG-inhibiting proteins (PGIPs; Di Matteo *et al*., 2003; Ferrari *et al*., 2012) have been described. Transgenic wheat plants expressing the bean *PvPGIP2* gene in their flowers showed significantly reduced symptoms in *F. graminearum*-incited FHB (Ferrari *et al*., 2012). Pectin methyl-esterification influences plant resistance, as PCW becomes less susceptible to fungal pectinases and endopolygalacturonases. The level of esterification in the PCW is controlled by a pectin methyl-esterase inhibitor (PMEI), supposed to confer resistance to the plant when demethylation is effectively inhibited. Wheat transgenic lines expressing *AcPMEI* from *Actinidia chinensis* showed reduced pectin methyl-esterase (PME) activity, and hence high pectin methylation levels and significantly reduced disease symptoms following inoculation with *F. graminearum* (Volpi *et al*., 2011). Recently, three PMEI genes have been identified and characterized in wheat (Rocchi *et al*., 2012), opening up new perspectives in the development of transgenic wheat lines potentially resistant to different *Fusarium* species, including *F. culmorum*.

Plants are able to chemically transform trichothecenes by their degradation or detoxification, or to reduce their accumulation by the inhibition of biosynthesis through the activity of endogenous compounds (Alabouvette *et al*., 2009; Bollina and Kushalappa, 2011; Boutigny *et al*., 2010; Yoshinari *et al*., 2008). Glycosylation represents the main plant-driven chemical transformation of mycotoxins in response to *Fusarium* attack (Karlovsky, 2011). In the naturally FHB-resistant wheat cultivar Sumai3, genetic mapping has revealed that the ability to detoxify DON by a DON glucosyltransferase colocalizes with a major quantitative trait locus (QTL) for FHB resistance (Lemmens *et al*., 2005). Transgenic *Arabidopsis thaliana* expressing a barley UDP-glucosyltransferase exhibited resistance to DON (Shin *et al*., 2012). Although several studies have been devoted to the selection of plant glycosylases, this does not appear to be an efficient strategy to control mycotoxin production, because of the possibility that glycosyl-protected mycotoxins may be re-converted into the original toxic form by hydrolysis in the digestive tract or during food/feed processing (the so-called 'masked' mycotoxins).

Some secondary plant metabolites, present in larger amounts in FHB-resistant plants, have been shown to inhibit fungal growth *in vitro* and/or mycotoxin production by *Fusarium* spp. These are phenolic and polyphenolic compounds belonging to the benzoic and cinnamic acids, furanocoumarins, phenylpropanoids, chromenes and flavones (Bakan *et al*., 2003; Boutigny *et al*., 2010; Mellon *et al*., 2012; Ojala *et al*., 2000; Takahashi-Ando *et al*., 2008; Wu *et al*., 2008). Most are constituents of PCW: in response to infection, plants release phenols from the cell wall in order to limit the pathogen spread by reinforcing plant structural components. Some dialkyl resorcinols and coumarins manifest antifungal activity against *F. culmorum* (Ojala *et al*., 2000; Pohanka *et al*., 2006). Moreover, phenols present anti-oxidant and/or radical scavenging activities (Kim *et al*., 2006). Therefore, defence mechanisms triggered in the plant in response to pathogenic oxidative processes involve the production of these secondary metabolites that can interfere in different ways with trichothecene biosynthesis.

OPTIONS FOR CONTROL

The multiple factors influencing fungal growth and trichothecene production by *F. culmorum* require the application of an integrated pest management approach, combining genetic, agronomic, chemical and biological control measures.

The growth of susceptible wheat varieties does not only increase the severity of FHB, but also the fungal biomass, with a consequent increase in the amount of toxins present in the harvested grain (Blandino *et al*., 2012; Snijders and Krechting, 1992; Tòth *et al*., 2008). The adoption of wheat cultivars showing resistance to primary infection and to the spread of the disease would be the ideal strategy. Unfortunately, there are no highly resistant wheat cultivars (Pereyra *et al*., 2004; Wisniewska and Kowalczyk, 2005). Nonetheless, extensive effort has been devoted to map the QTLs associated with FHB resistance in wheat (see, for example, Häberle *et al*., 2009; Schmolke *et al*., 2008). Genotypes bearing resistance to FHB have been reported and it is encouraging that resistance of a given genotype is not specific to a single *Fusarium* species, but can be extended to all the causative agents of this disease (Mesterhazy *et al*., 2005; Miedaner *et al*., 2012).

Being a typical seed-borne pathogen, *F. culmorum* survives on or within the infected seed, which remains the main cause of pre- or post-emergence seedling death, and contributes to increase the inoculum potential in the soil. Consequently, ploughing should be preferred to direct sowing or minimum tillage practices, which favour inoculum survival (Blandino *et al*., 2012; Dill-Macky and Jones, 2000; Miller *et al*., 1998; Teich and Nelson, 1984). Similarly, crop rotation with noncereal host crop intermediates, such as legumes, alfalfa and Brassicaceae, may reduce the incidence of disease (Kurowski *et al*., 2011; Parry *et al*., 1995). The use of healthy seed coated with fungicides represents a most efficient means of control, but is usually limited to the early stages of the wheat cycle, as fungicides do not maintain their efficiency over a longer period. To improve the slow release of the delivered compound, a tebuconazole–β-cyclodextrin inclusion complex has been proposed for the control of FRR during the early stages of durum wheat growth (Balmas *et al*., 2006).

Several fungicides, mainly belonging to the azole (bromuconazole, cyproconazole, metconazole, prochloraz, propiconazole, prothioconazole and tebuconazole) and strobin (azoxystrobin) classes, have been shown to control the disease by up to 70% in the field and to reduce the amount of mycotoxins in kernels; this is particularly evident under low disease pressure or on wheat genotypes possessing moderate resistance (Chala *et al*., 2003; Jones, 2000; Menniti *et al*., 2003; Paul *et al*., 2008). However, an increase in mycotoxin content in the kernel can occur when fungicides are applied at sublethal concentration or if they differ in their activity against distinct *Fusarium* pathogens (Covarelli *et al*., 2004; Gardiner *et al*., 2009; Gareis and Ceynowa, 1994; Haidukowski *et al*., 2005; Hysek *et al*., 2005; Matthies and Buchenauer, 2000; Matthies *et al*., 1999; Ochiai *et al*., 2007; Simpson *et al*., 2001; Stack, 2000). Moreover, the prolonged use of molecules sharing the same mode of action may induce a selective pressure on the pathogenic fungal populations, enabling the selection of resistance traits. Resistance to trifloxystrobin (a complex III respiration inhibitor) and isopyrazam (a complex II respiration inhibitor) has been reported recently on two isolates within two different chemotypes (Pasquali *et al*., submitted). These results have been confirmed on a larger set of isolates collected in Luxembourg (M. Beyer, Centre de Recherche—Gabriel Lippmann, Belvaux, Luxembourg , personal communication), suggesting that, as in the case of *F. graminearum*, these resistance traits are of natural origin (Dubos *et al*., 2011, 2013).

An alternative approach to minimize the risk of resistance among fungal populations relies on the use of new molecules, based on the structure of natural and natural-like inhibitors, able to counteract the pathogenic and mycotoxigenic potential of natural populations of *Fusarium*, rather than acting on their saprophytic phase, or capable of stimulating natural resistance responses by the host plant. Essential oils of plant origin and some natural monoterpenes, considered as 'Generally Recognized As Safe' (GRAS) chemicals (safe for food use), have both inhibitory effects against mycotoxin biosynthesis and fungicide activity (Dambolena *et al*., 2008; Ellouze *et al*., 2012; Yaguchi *et al*., 2009). In particular, extracts from malva, chamomile and citrus manifest fungistatic activity against *F. culmorum* (Ellouze *et al*., 2012; Magro *et al*., 2006).

A specific and powerful inhibitory activity has been demonstrated by phenolic and polyphenolic natural compounds (Bakan *et al*., 2003; Boutigny *et al*., 2010; Desjardins *et al*., 1988; Takahashi-Ando *et al*., 2008). The most abundant phenols extracted from maize kernel pericarp and wheat bran are *trans*-ferulic acid and the corresponding dehydrodimers (DFAs), namely dehydrodiferulates (Bily *et al*., 2003; Boutigny *et al*., 2008; Kim *et al*., 2006). Hydroxycinnamic acids are known to be major components of the primary cell wall of cereals (Bakan *et al*., 2003). These compounds are ester bound to the C5 hydroxyl of the arabinosyl side chain of cell wall arabinoxylan chains. The feruloyl residues, predominant species, can also be dimerized under an oxidative coupling mediated by POXs, form cross-links or dehydrodimers of ferulic acid, and then lead to a reinforcement of the primary wall of the plant.

A phenolic fraction rich in these phenolic acids manifested a drastic reduction on *in vitro* DON and ADON biosynthesis by *F. culmorum* (Boutigny *et al*., 2010). Although the mechanism remains unclear, it is reasonable to hypothesize that these compounds, mainly DFAs, interfere with *in vitro* cell wall degradation by fungal hydrolases. The activity of fungal esterases, overexpressed during growth on host tissues, can release free forms of ferulic ester from cell wall tissues (Balcerzak *et al*., 2012; Jaroszuk-Scisel *et al*., 2011). Once released, free ferulate may inhibit the ability of *Fusarium* to produce mycotoxins. One of the DFAs present in the phenolic acid mixture, 8,5′-benzofuran dimer, shows the same inhibitory activity of ferulic acid against *F. culmorum*, although a synergism of the phenolic acid mixture may play a crucial role in the inhibition of mycotoxins (Boutigny *et al*., 2010).

The X-ray crystal structure of trichodiene synthase, purified from *F. sporotrichioides* and complexed with Mg^{2+}(three ions)-inorganic pyrophosphate (PPi), provides critical details regarding the molecular recognition of PPi, giving further insights into the trichothecene pathway, and therefore on the possibility of using external ligands able to interfere with mycotoxin production (Rynkiewicz *et al*., 2001; Vedula *et al*., 2008). The combination of bioprospecting and computational studies offers a useful way to select and investigate new natural and natural-like mycotoxin inhibitors and fungicides against *Fusarium*. A collection of natural and natural-like phenols and dimers was recently correlated with their ability to inhibit *in vitro* 3-ADON and DON in *F. culmorum* and to interact with the trichodiene synthase crystal structure (G. Delogu, Istituto CNR di Chimica Biomolecolare, Sassari, Italy, unpublished data).

The susceptibility of the model plant *A. thaliana* to both *F. graminearum* and *F. culmorum* infection (Urban *et al*., 2002)

Table 4 Biological control agents developed to control *Fusarium culmorum* infection on wheat.

Antagonist	Target disease	Application method	Reference
Chaetomium sp. *Idriella bolleyi* *Gliocladium roseum*	FRR	Seed coating (field)	Knudsen *et al*. (1995)
Alternaria alternata *Botrytis cinerea* *Cladosporium herbarum*	FHB	Spray at ear emergence complete or anthesis complete (glasshouse)	Liggitt *et al*. (1997)
Trichoderma harzianum	FRR	Seed coating (field)	Michalikova and Michrina (1997)
Trichoderma harzianum *Trichoderma atroviride* *Trichoderma longibrachiatum* *Gliocladium roseum* *Penicillium frequentans*	FRR, FHB	Seed coating (field)	Roberti *et al*. (2000)
Gliocladium roseum (*Clonostachys rosea*)	FRR FRR	Seed coating (field) Seed coating (*in vitro*)	Jensen *et al*. (2000); Roberti *et al*. (2008)
Phoma betae	FHB	Spray at early anthesis (glasshouse)	Diamond and Cooke (2003)
Pseudomonas fluorescens *Pantoea agglomerans*	FRR	Seed coating (glasshouse and field)	Johansson *et al*. (2003)
Fusarium equiseti	FHB	Spray at anthesis (field)	Dawson *et al*. (2004)
Bacillus mycoides	FRR	Seed coating (microplot)	Czaban *et al*. (2004)
Different filamentous fungi and yeasts	FRR, FHB	Wheat straw (*in vitro*)	Luongo *et al*. (2005)
Pseudomonas fluorescens *Pseudomonas frederiksbergensis*	FHB	Spray at mid-anthesis (glasshouse and field)	Khan and Doohan (2009); Petti *et al*. (2008)
Streptomyces sp.	FRR	Seed coating (glasshouse)	Orakci *et al*. (2010)
Bacillus subtilis	FRR	Seed coating (glasshouse)	Khezri *et al*. (2011)
Trichoderma gamsii	FRR, FHB	Wheat haulms and rice kernels (*in vitro*)	Matarese *et al*. (2012)

has opened up new possibilities of developing high-throughput experimental approaches to select new protecting compounds. Working with *F. graminearum*, Schreiber *et al*. (2011) identified small molecules, such as sulphamethoxazole and the indole alkaloid gramine, that protect *Arabidopsis* seedlings from infection. The same chemicals reduced significantly the severity of *F. graminearum* infection in wheat (Schreiber *et al*., 2011).

The integration of biological control approaches may offer an effective support to *F. culmorum* management on wheat and other cereals. The flag leaf and ripening ear surfaces of wheat are colonized by a panoply of micro-organisms whose numbers may vary with plant growth stage and environmental conditions (Magan and Lacey, 1986). The application of natural antagonists to the crop residues or directly onto plant organs by spray or by seed dressing achieved reduced severity of FRR or FHB by *F. culmorum* on wheat, and the contamination of grain with mycotoxins (Table 4).

FUNCTIONAL GENOMICS

The *F. culmorum* genome is largely unknown. On analysis of the National Center for Biotechnology Information (NCBI) database for proteins associated with *F. culmorum*, 189 hits were returned on 15 November 2012. Annotated proteins include elongation factor 1α, a putative reductase, the RNA polymerase II, a phosphate permease, a putative regulatory protein used for phylogenetic analysis (Ward *et al*., 2002) and genes of the *TRI* cluster, involved in the synthesis of trichothecenes, also used for phylogenetic studies. Other *F. culmorum* annotated proteins include an ABC transporter (Skov *et al*., 2004), the trichodiene synthase used for RNA silencing experiments (Scherm *et al*., 2011), three putative allergenic proteins (Hoff *et al*., 2003), hydrophobin precursors involved in gushing (Stübner *et al*., 2010) and further proteins involved in the foam effect in beers (Zapf *et al*., 2007), and a fragment of a polyketide synthase essential in zearalenone biosynthesis (Atoui *et al*., 2012). Other genes have also been cloned in *F. culmorum* whilst studying the production of secondary metabolites, such as the nonribosomal peptide synthetase NPS2 able to synthesize ferricrocin (Tobiasen *et al*., 2007). Proteinases have also been isolated from *F. culmorum* (Levleva *et al*., 2006).

Functional characterization of the genes involved in the pathogenic process in *F. culmorum* is even more limited. Genetic transformation of the fungus is well established (Doohan *et al*., 1998), but the lack of a full genome has limited the functional analysis of genes to a few examples. Scherm *et al*. (2011) demonstrated that RNAi silencing as a functional approach is working in *F. culmorum*. Silencing of the zinc finger transcription factor *TRI6*, using inverted repeat transgenes, led to significantly decreased expression rates of the trichodiene synthase encoding gene *TRI5* and, consequently, to a decline in DON production. Hence, trichothecene production of *F. culmorum* is tightly related to its aggressiveness and virulence in determining the symptoms of FRR on wheat (Scherm *et al*., 2011).

A second gene shown to play a role in pathogenesis is an ABC transporter, FcABC1, supposed to confer resistance to defensive compounds produced by the plant during the head infection

process in wheat (Skov *et al*., 2004). The *FcABC1* deletion mutant was unaltered in its physiology, but showed up to 98% reduced aggressiveness compared with the wild-type strain, suggesting that the ability to excrete secondary plant metabolites allows *F. culmorum* to overcome the inhibition of host tissue invasion (Skov *et al*., 2004).

An *F. culmorum* topoisomerase I gene (*top1*) was found by a random plasmid insertional mutagenesis approach in *F. graminearum* and deleted in *F. culmorum* (Baldwin *et al*., 2010). The deletion mutant showed a complete block of conidia production as a result of its inability to regulate the transcriptional changes required for perithecial development. Furthermore, the mutant showed a significantly reduced virulence in wheat ear infection with low ability to colonize tissues after penetration (Baldwin *et al*., 2010).

The role of the gene *FcStuA*, a *stuA* orthologue protein with an APSES domain sharing 98.5% homology to the FgStuA transcription factor (FGSG10129) of *F. graminearum* (Lysøe *et al*., 2011), was recently determined by the functional characterization of deletion mutants. *FcStuA* was found to completely control pathogenicity and to reduce significantly (but not by blocking as in *F. graminearum*) DON production in *F. culmorum* mutants, together with a strong impairment of conidiation and significant morphological changes (M. Pasquali, Centre de Recherche—Gabriel Lippmann, Belvaux, Luxembourg, personal communication).

Given the very limited number of genes described to be involved in the pathogenic process in *F. culmorum*, further instruments and approaches are needed to explore the pathogenic arsenal of the fungus. A forward genetic tool based on a transposon insertion screening in the genome of *F. culmorum* (Spanu *et al*., 2012) did not lead to the identification of FRR *PR* genes, but allowed the isolation of partial sequences of aurofusarin genes and other genes involved in oxidative stress resistance, and the partial mapping of this unknown genome by the generation of more than 50 000 bp of *F. culmorum* sequence.

The availability of genomes would facilitate targeted functional genomics studies that, at the moment, are based on the similarities of genes with *F. graminearum* (Baldwin *et al*., 2010), but this cannot explore genes that are peculiar to *F. culmorum* (Spanu *et al*., 2012).

It is quite opportune that two *F. culmorum* genome sequencing programmes are on their way to being released. The first involves *F. culmorum* isolate FcUK99 (NRRL 54111; FGSC 10436), recovered from an infected wheat ear in the UK in 1998 (Baldwin *et al*., 2010). This isolate is fully pathogenic on wheat ears, tomato fruits and *Arabidopsis* floral tissue, and produces DON and 3-ADON. By 454 sequencing, a 13.4× coverage of the *F. culmorum* isolate FcUK99 genome has been generated. In addition, four normalized cDNA libraries have been Illumina sequenced to give a transcriptome coverage of 100× (6 Gb of data). The *F. culmorum* genome size is estimated to be 39 Mbp, i.e. slightly larger than *F. graminearum*. In addition, the draft genomes of a further three *F. culmorum* isolates with different biological properties have been generated by sequencing with Illumina technology using 100-bp pair-end reads (M. Urban, J. Antoniw, N. Hall and K. E. Hammond-Kosack, Wheat Pathogenomics, Plant Biology and Crop Sciences Department, Rothamsted Research, Harpenden, Herts, UK, personal communication).

As part of a larger programme of sequencing of the genomes of cereal *Fusarium* pathogens causing crown rot disease using Illumina paired-end sequencing (see Gardiner *et al*., 2012), Donald Gardiner and John Manners at the Commonwealth Scientific and Industrial Research Organization (CSIRO, Clayton, Vic., Australia), together with Bioplatforms Australia (Sydney, NSW, Australia), have obtained sequence information for another isolate of *F. culmorum*, obtained from infected crown tissue of a wheat plant grown in Western Australia. Genome coverage will be >30-fold and sequence information will be made publicly available early in 2013 on an Australian-based website, and ultimately published on the NCBI site (J. M. Manners, CSIRO, Clayton, Vic., Australia, personal communication).

FUTURE CHALLENGES

Although it is not yet regarded as a 'model system', the *F. culmorum*–wheat interaction presents several features allowing it to be considered as a tractable model for investigation. Sequencing data permit a comparison of *F. culmorum* with other species whose genome information has already been released. One of the future challenges of genomics research will be to identify the peculiarities of this species involved in environmental adaptation and toxigenic and pathogenic potential compared with the closely related *Fusarium* spp. Many fundamental questions remain open. Has *F. culmorum* indeed lost its sexual cycle? What favours the shift in the *F. culmorum/F. graminearum* ratio in cereals? What is the role of nonpathogenic populations of *F. culmorum* in conferring adaptation to their host plants and how do saprophytic strains differ from pathogenic strains? Knowledge on the *F. culmorum* chemotype distribution worldwide may help us to better understand how chemotypes can be favoured by certain agroclimatological conditions. Given the general lack of information on the chemotype from the Southern Hemisphere and from worldwide populations of *F. culmorum*, it would be worth studying the chemotype distribution in relation to the host and to the disease phases (i.e. FHB or FRR), and comparing this with isolates obtained from undisturbed soils, in order to decipher the role of the chemotype in the presence versus absence of agricultural selection environments.

Finally, the identification of new natural and natural-like molecules inhibiting trichothecene biosynthesis by *F. culmorum*, without affecting its vegetative growth, presents a vast array of practical applications. The bioavailability of inhibiting molecules

and the evidence that exposure *in vitro* to different concentrations may result in opposite effects (i.e. inhibition versus enhancement of trichothecene production; G. Delogu, unpublished data) may prompt the development of new ecofriendly formulations to reduce the risk of these compounds being strongly affected by environmental conditions when applied in the field.

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