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REVIEW

Deoxynivalenol resistance as a component of FHB resistance

L. R. Gunupuru[1] · **A. Perochon**[1] · **F. M. Doohan**[1]

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Abstract Fusarium head blight (FHB) is one of the most devastating diseases of wheat (*Triticum aestivum*), barley (*Hordeum vulgare*) and other small grain cereals grown in warm and humid regions worldwide. In addition to yield loss, the disease compromises the quality of infected grain as a result of contamination with a range of *Fusarium* mycotoxins that are harmful to human and animal health. Deoxynivalenol (DON) is the most prevalent trichothecene mycotoxin found in *Fusarium*-infected grains. DON acts as a virulence factor for *Fusarium*, facilitating disease spread within wheat heads. Resistance to DON is an innate component of FHB resistance. Here we review FHB as a globally important disease, with a specific focus on the role of DON in disease development, the importance of its' resistance in plant defence against *Fusarium* and the current knowledge regarding the genes activated as part of the cereal defence against the toxin.

Keywords Barley · Deoxynivalenol (DON) · *Fusarium culmorum* · *Fusarium graminearum* · Fusarium head blight (FHB) · *Fhb1* · Multi-drug resistance (MDR) ABC transporter · Plant resistance · UDP-glucosyltransferase (UGT) · Wheat

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✉ F. M. Doohan
fiona.doohan@ucd.ie

[1] Molecular Plant-Microbe Interactions Laboratory, UCD School of Biology and Environmental Science and UCD Earth Institute, University College Dublin, Dublin, Ireland

Introduction

Fusarium head blight (FHB) is a devastating disease of small grain cereals caused by *Fusarium* spp. that reduce the yield and contaminates grain with mycotoxins that are harmful to human and animal health (Desjardins 2006; Osborne and Stein 2007; Mohanty et al. 2013). Many FHB outbreaks have been reported across Europe, America and Asia during the 20 and 21st centuries (Elias et al. 2005; Oliver et al. 2007; McMullen et al. 2012; Giroux et al. 2016). Although many species of *Fusarium* can cause FHB, the most common causal agents are *Fusarium graminearum* Schwabe and *Fusarium culmorum* Saccardo (Schroeder and Christensen 1963; Bai and Shaner 1994, 2004). The fungus infects wheat heads during flowering and thereby interferes with seed development, leading to shrivelled grains that may be light enough to be expelled with chaff during harvesting. The fungus destroys starch granules, storage proteins and cell walls during the invasion of grains (Bechtel et al. 1985). *Fusarium* spp. that infect cereal crops are able to produce several mycotoxins, but the toxin most associated associated with FHB epidemics is deoxynivalenol (DON), which belongs to a large family of mycotoxigenic sesquiterpene ep-oxides, namely the trichothecenes and it is commonly found in grain from FHB-diseased cereal heads. This review provides an overview on the deleterious effects of DON, its role in disease development and current knowledge regarding the genes activated as part of the cereal defence against the toxin.

The deleterious effects of DON

Trichothecenes inhibit protein biosynthesis by binding to the 60S subunit of eukaryotic ribosomes and inhibiting either the chain initiation, elongation or termination steps of protein

synthesis. Either as a consequence of this, or additional to this, they also cause lipid peroxidation, programmed cell death (apoptosis), ribotoxic stress, inhibition of DNA synthesis, disruption of membrane integrity and inhibition of cell division (Schindler 1974; Carter and Cannon 1977; Azcona-Olivera et al. 1995; Shifrin and Anderson 1999; Kouadio et al. 2005; Arunachalam and Doohan 2013). Numerous studies have demonstrated the negative effects of DON consumption on both human and animal health. DON can cause feed refusal, weight loss and death (Eriksen and Pettersson 2004; Arunachalam and Doohan 2013). In farm animals, the induction of apoptotic lesions in liver and in lymphoid tissues was observed in pigs exposed to DON (Mikami et al. 2010). Depending on cell type and concentration, DON can act as either an immunostimulant or an immunosuppressor (Pestka and Smolinski 2005). Waché et al. (2009) reported the dose-dependent suppression of the cell surface markers CD54, CD14, CD119 and HLA-DP/DQ/DR in human macrophages when cells were treated with DON; these cellular markers play a major role in cell signalling and antigen presentation during the immune response. As a result of their acute toxicity in humans and animals, several countries, including the European Union (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1881&from=en) and the United States Food and Drug Administration (U.S. FDA) (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ChemicalContaminantsMetalsNaturalToxinsPesticides/ucm120184.htm) have set the tolerable human and animal daily intake (TDI) levels for DON in cereal and their derivative products.

The role of DON in disease development

F. graminearum is a hemibiotroph, with a short biotrophic phase preceding necrotrophism (Trail 2009). During the biotrophic phase, which is estimated to continue 24 to 32 h after infection (Gottwald et al. 2012), the fungus feeds off living host cells. Fungal conidia and ascospores begin to germinate 6–12 h after the initial contact, and the emergent germ tube gives rise to hyphae that will enter the host through stomata or other susceptible sites; thereafter the fungus grows and extends on the interior surface to form dense mycelial networks (Kang and Buchenauer 2000; Xu and Nicholson 2009). From the point of infection, the hyphae can reach the adjacent florets and spikelets by two routes: either internally via vascular bundles or externally via stomata. When the environmental conditions are optimum for the growth of fungus (high humidity and a warm temperature), the hyphae may penetrate into the rachis and rachilla, and disease will spread up and downwards within the head through the vascular bundles and parenchyma (Kang and Buchenauer 2000; Lewandowski and Bushnell 2001; Bushnell et al. 2003; Goswami and Kistler 2004,). Mycelium may also spread on the surface of glumes from the infected spikelet to healthy ones (Ribichich et al. 2000). The growing fungal mycelium can block the vascular bundle cells in the rachis, preventing the movement of water and nutrients to the head and thus inducing the classic FHB phenotypic symptoms, i.e. the premature bleaching of heads and shrivelling of grains (Xu and Nicholson 2009).

DON is a fungal virulence factor that facilitates disease spread within wheat heads (Bai et al. 2002). Production of DON is typically observed 24 h post-inoculation (Chen et al. 1995), with a significant increase in levels by 96 h (Savard et al. 2000). The switch to necrotrophy is associated with an increase in DON production (Boddu et al. 2006; Walter et al. 2010). DON can be transported through vascular elements, upwards and downwards, to the neighbouring healthy spikelets (Kang and Buchenauer 1999). Varying concentrations of DON (1–100 ppm) elicited a wide range of defence responses in wheat leaves, including hydrogen peroxide accumulation and programmed cell death (PCD) (Desmond et al. 2008). Interestingly, Diamond et al. (2013) showed that both 10 ppm DON and a DON-producing strain of *F. graminearum* prevented heat-induced PCD in *Arabidopsis* cell cultures. They speculated that the suppression of PCD by low levels of DON might facilitate pathogen establishment in the initial biotrophic phase of *Fusarium* infection whereas higher level of DON may support the necrotrophic phase of the disease that ultimately leads to the appearance of the FHB disease symptoms. These symptoms typically manifest as premature bleaching of wheat spikelets but can also include the appearance of water-soaked brown, dark purple to black coloured necrotic lesions on the exterior surface of the florets. Like FHB, DON has also been shown to cause premature bleaching of plant tissue: it causes premature bleaching of both wheat heads and barley leaf tissues (Bushnell et al. 2003, 2010; Lemmens et al. 2005; Schweiger et al. 2010; Diamond et al. 2013). Application of DON to the central spikelets of wheat heads led to the premature bleaching of florets in both the antipetal and basipetal direction (Lemmens et al. 2005; Ansari et al. 2007).

Host resistance to FHB

Wheat cultivars differ in their response to FHB; some are more resistant, some are highly susceptible, but no genotype is immune. Resistance is horizontal, i.e. it is not considered *Fusarium* species-specific (Van Eeuwijk et al. 1995), but it is quantitative, polygenic and can be affected by the environment (Bai and Shaner 2004). Several components or 'types' of FHB resistance have been described, but types I and II are most widely accepted. Type I is defined as resistance to initial infection and type II as resistance to pathogen spread within

the spike (Schroeder and Christensen 1963; Mesterhazy 1995). Other types of FHB resistance include resistance to kernel infection (type III), tolerance to FHB and DON (type IV) and resistance to DON accumulation (type V) (Boutigny et al. 2008). Type V resistance has also been divided into two subclasses to delineate processes that chemically modify trichothecenes (class 1) from processes that reduce the accumulation of trichothecenes (class 2) (Boutigny et al. 2008). Many people consider Type V as a subcomponent of type II resistance because it reduces the spread of disease.

Genetic loci linked to DON detoxification

Many quantitative trait loci (QTL) have been identified that contribute to different types of FHB resistance in wheat (Prat et al. 2014). Many FHB resistance QTL have also been associated with low DON accumulation (Somers et al. 2003; Ma et al. 2006). But few have been tested for their ability to either detoxify DON or enhance resistance to the toxin. Somers et al. (2003) mapped QTL controlling FHB resistance and DON accumulation in a double haploid population derived from a cross between cultivars Wuhan-1 and Nyubai. They reported QTL on chromosomes 2DS and 5AS that control the accumulation of DON, and they showed that this association was independent of FHB resistance. QTL *Fhb1* was the first major QTL discovered for type II resistance and it was identified on chromosome 3B of cv. Sumai-3 (Bai et al. 1999; Anderson et al. 2001; Zhou et al. 2002; Cuthbert et al. 2006). The first functional characteristic to be linked to *Fhb1* QTL was reported by Lemmens et al. (2005), whereby plants carrying *Fhb1* were more resistant to DON-induced bleaching and were able to convert DON into a less toxic derivate, DON-3-*O*-glucoside (D3G). As will be discussed below, UDP-glycosyltransferases (UGTs) can convert DON to D3G (Poppenberger et al. 2003). Based on the sequenced cv. Chinese Spring genome, several UGTs have been annotated in a contig that contains the QTL *Fhb1* region of cv. Sumai-3 (Choulet et al. 2010). But the first *Fhb1*-encoded gene conclusively linked to FHB resistance does not encode a UGT. Recently, using a combination of mutation analysis, gene silencing and transgenic overexpression, a gene within *Fhb1* was shown to confer FHB resistance (Rawat et al. 2016). It encodes a pore-forming toxin-like protein (PFT) with a chimeric lectin and an ETX/MTX2 toxin domain. Surprisingly, they showed that *PFT* does not play a role in DON detoxification and suggested that the DON detoxification locus is near the same genetic block. Thus, it may be that the association between QTL *Fhb1* and DON detoxification is due to either genetic linkage or the manifestation of downstream regulatory effects of the locus. This warrants further investigation.

Genes that directly effects DON resistance and/or DON detoxification

Table 1 outlines examples of genes directly involved in DON resistance and/or DON detoxification. As stated above, UGTs have been shown to convert DON to less toxic DON-3-G (Poppenberger et al. 2003). Overexpression of the *UGT* gene *DOGT1* in *Arabidopsis* enhanced the conversion of DON to less toxic DON-3-G (Poppenberger et al. 2003). This discovery was a major breakthrough with regard to advancing DON detoxification strategies and it stimulated the search for cereal UGTs that had the same biochemical potential. A wheat *UGT* similar to *DOGT1, TaUGT3,* could enhance DON tolerance when expressed in *Arabidopsis* (Lulin et al. 2010). Wheat *UGT* gene *TaUGT12887* provided weak DON tolerance when expressed in a toxin sensitive yeast strain (Schweiger et al. 2013b). Transgenic *Arabidopsis* lines expressing a barley

Table 1 Genes that contribute to DON resistance and/or DON detoxification

Gene annotation	Gene	Reference
Cytochrome P450	*Ddna*	Ito et al. 2013
Ethylene Insensitive 2	*EIN2*	Chen et al. 2009
Gibberellic acid sensitive DELLA protein	*TaRht-B1b* and *TaRht-D1b*	Saville et al. 2012
Methionyl-tRNA synthetase	*TaMetRS*	Zuo et al. 2016
Multi-drug resistance ABC transporter	*ScPDR5*	Mitterbauer and Adam 2002
	TaABCC3.1	Walter et al. 2015
UDP-glucosyltransferase	*DOGT1*	Poppenberger et al. 2003
	TaUGT3	Lulin et al. 2010
	HvUGT13248	Shin et al. 2012; Li et al. 2015
	Bradi5g02780; Bradi5g03300	Schweiger et al. 2013a; Pasquet et al. 2016
	TaUGT12887	Schweiger et al. 2013b
Unknown function	*TaFROG*	Perochon et al. 2015

UGT (HvUGT13248) showed enhanced tolerance to DON toxicity (Shin et al. 2012). Li et al. (2015) went on to demonstrate that the expression of this barley gene in transgenic wheat rapidly and efficiently conjugated DON to D3G and generally reduced the severity of FHB under field conditions. The model cereal *Brachypodium distachyon* encodes two homologs of *HvUGT13248*, and the encoded proteins were shown to convert DON to D3G when expressed in yeast (Schweiger et al. 2013a). Overexpression of *Brachypodium* UGT *Bradi5g03300* reduced the toxicity of DON towards root tissue and enhanced spikelet resistance to FHB disease (Pasquet et al. 2016).

Several other microbial and plant genes, including cereal genes, have been shown to directly affect DON resistance. These include genes encoding detoxification enzymes, transporters, tRNA synthesis, regulators of hormones signalling and proteins of unknown function (Table 1). Multidrug resistance (MDR) ABC transporters genes encoding yeast pleiotropic drug transporter 5 (PDR5) and the wheat ABCC transporter protein TaABCC3.1 were shown to contribute to DON tolerance. Deletion of a yeast *PDR5* gene increased sensitivity to growth inhibition caused by DON and expression of the yeast gene in tobacco increased DON resistance (Mitterbauer and Adam 2002). *TaABCC3.1* was shown to contribute to DON tolerance in wheat, as determined via enhanced DON bleaching of spikelets in plants in which the gene was silenced (Fig. 1; Walter et al. 2015). While PDR5 is likely to act as a molecular efflux pump, removing toxic substances, the function of TaABCC3.1 is unknown.

Enzymes involved in diverse processes have been shown to enhance DON resistance. Expression of a wheat DON-activated methionyl-tRNA synthetase gene (*TaMetRS*) in *Arabidopsis* enhanced seedling resistance towards DON and floret resistance towards *Fusarium* (Zuo et al. 2016). The bacterial cytochrome P450 *Ddna* was showed to convert DON to 16-hydroxy-DON (16-HDON) (Ito et al. 2013). When the hydroxylated 16-HDON product was tested on wheat seedlings the seedlings did not show any reduction in shoot length and fresh weight, indicating the hydroxylated product is a non-toxic DON metabolite (Ito et al. 2013). Phytohormones play a major role in plant defence against biotrophic and necrotrophic pathogens. Doohan et al. (2008) speculated that maintenance of hormone homeostasis plays an important role in DON tolerance. Chen et al. (2009) demonstrated the role of ethylene signalling in DON-induced PCD. Silencing of a gene encoding Ethylene Insensitive 2 (*EIN2*) in wheat resulted in FHB resistance and reduced DON-induced PCD in leaves. Moreover the gain of function (GoF) of gibberellic acid sensitive (GA) DELLA NIL lines *Rht-B1b* and *Rht-B1c* showed more resistance to *Fusarium* infected spikes and DON associated bleaching compare to taller counter parts *rht-tall* NIL

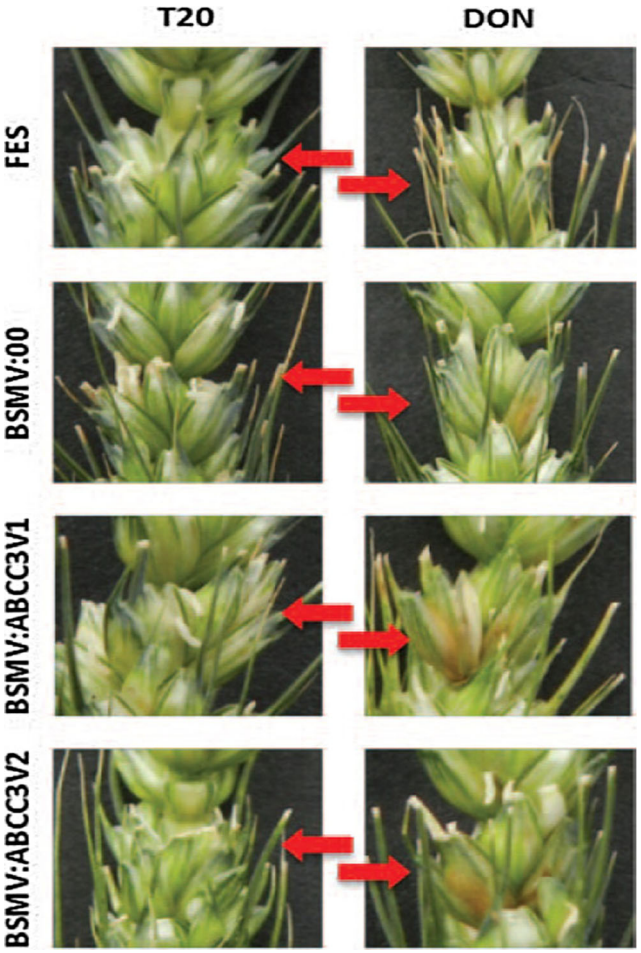

Fig. 1 Virus Induced Gene Silencing (VIGS) of the multi-drug resistance (MDR) ABC transporter *TaABCC3.1* in wheat heads resulted in more DON-induced bleaching of spikelets (Walter et al. 2015). Treatments: FES (buffer control), BSMV:00 (empty virus vector), BSMV:ABCC3V1 (silencing construct 1), BSMV:ABCC3V2 (silencing construct 2), T20 (Tween-20), DON (deoxynivalenol)

lines. Both the NIL lines *Rht-B1b* and *Rht-B1c* also showed reduced lesion lengths and DON induced cell death than *rht-tall* lines (Saville et al. 2012).

There is increasing evidence that organisms have evolved taxonomically restricted 'orphan' genes to help them overcome environmental stress (Arendsee et al. 2014; Perochon et al. 2015). DON resistance research has contributed to our understanding of cereal evolution in that a *Pooideae*-restricted gene was discovered based on its responsiveness to the toxin. Perochon et al. (2015) characterised *TaFROG,* which is the wheat homolog of a *Pooideae*-specific gene, and demonstrated that overexpression of this gene enhanced DON and FHB resistance in wheat. Additionally, gene silencing of *TaFROG* resulted in more DON associated bleaching of wheat spikelets in the DON resistant wheat cv. CM82036 (Perochon et al. 2015). Ongoing studies are trying to delineate other orphan genes involved in wheat resistance to disease, including FHB disease.

Genes associated with DON resistance and the DON response

Table 2 outlines examples of the wheat genes that have been associated with DON resistance and DON production by *F. graminearum*. Comparative transcript analysis studies using near isogenic or double haploid lines that segregated for *Fhb1* identified several genes associated, at the transcriptional level, with either *Fusarium* or DON resistance conferred by QTL *Fhb1* (Buerstmayr et al. 2003; Ansari et al.

Table 2 Wheat genes associated with DON resistance and the DON response

Gene annotation	Stimulant[a]	Wheat cultivar[b]	Reference
Cellular metabolism			
AAA^+ ATPase Zinc binding alcohol dehydrogenase	DON vs Tween-20	'CM82036' (R) vs 'Remus' (S), DH lines	Walter et al. 2008
O-methyltransferase Tetratricopeptide repeat protein	DON vs Water; *F. g* (WT) vs Water	RI 63 (R) vs MN97448 (S), NIL lines	Hofstad et al. 2016
Detoxification			
Glutathione S-transferase	DON vs Water;	GS-1-EM0040 and GS-1-EM0168 (R) vs 'Superb' (MS)	Foroud et al. 2012
	F. g (WT) vs Water	RI 63 (R) vs MN97448 (S), NIL lines	Hofstad et al. 2016
UDP-glycosyltransferase	DON vs Tween-20	'CM82036' (R) vs 'Remus' (S), DH lines	Walter et al. 2008
	DON vs Water; *F. g* (WT) vs Water	RI 63 (R) vs MN97448 (S), NIL lines	Hofstad et al. 2016
Kinases			
CDPK-related protein kinase Nucleoside diphosphate kinase III	DON vs Water; *F. g* (WT) vs Water	GS-1-EM0040 and GS-1-EM0168 (R) vs 'Superb' (MS)	Foroud et al. 2012
Phytosulfokine LRR receptor kinase			
Protein kinase 1			
Putative MAPKKK			
Serine/threonine protein kinase			
Serine/threonine kinase receptor-associated protein			
Receptor-like protein kinase		RI 63 (R) vs MN97448 (S) NIL lines	Hofstad et al. 2016
Oxidoreductases			
Alternative oxidase	DON vs Tween-20	'CM82036' (R) vs 'Remus' (S), DH lines	Walter et al. 2008
Cytochrome P450s	DON vs Tween-20	'CM82036' (R) vs 'Remus' (S), DH lines	Walter et al. 2008
	DON vs Water	'Sumai3' (R) vs 'Annong8455' (S)	Li et al. 2010
	F. g (WT) vs Water	RI 63 (R) vs MN97448 (S), NIL lines	Hofstad et al. 2016
Peroxidase	DON vs Tween-20	'CM82036' (R) vs 'Remus' (S), DH lines	Ansari et al. 2007
Programmed Cell Death			
Bax Inhibitor-1 Radical Induced Cell Death 1	DON vs Water	*Rht-tall*, *Rht-B1b*, *Rht-B1c.* NIL lines	Saville et al. 2012
Retrotransposons			
Long terminal repeat of an Erika retrotransposon Poly protein of a Romani retrotransposon	DON vs Tween-20	'CM82036' (R) vs 'Remus' (S), DH lines	Ansari et al. 2007
Transporter proteins			
Mitochondrial phosphate transporter	DON vs Tween-20	'CM82036' (R) vs 'Remus' (S), DH lines	Walter et al. 2008
Multi-drug resistance ABC transporter	DON vs Tween-20	'CM82036' (R) vs 'Remus' (S), DH lines	Walter et al. 2015
	DON vs Water; *F. g* (WT) vs Water	RI 63 (R) vs MN97448 (S), NIL lines	Hofstad et al. 2016
Unknown function			
Orphan gene (*TaFROG*)	DON vs Tween-20; *F. g* (WT) vs *F. g* (Mu)	'CM82036' (R)	Perochon et al. 2015

[a] *F. g (WT) F. graminearum* wild type, *F. g (Mu) F. graminearum* DON-minus mutant, *DH* double haploid lines, *NIL* near isogenic lines

[b] *R* resistant cultivar, *S* susceptible cultivar, *MS* moderately susceptible cultivar

2007; Walter et al. 2008, 2015; Jia et al. 2009; Schweiger et al. 2013b, 2016). The genes linked to *Fhb1* are involved in numerous defence responses in plants, including pathogenesis-related (PR) proteins, the synthesis of antimicrobial compounds, antioxidative stress responses, DON detoxification, cell morphogenesis and cell wall fortification (Walter and Doohan 2011; Foroud et al. 2012; Schweiger et al. 2016). Walter et al. (2008) investigated the transcriptomic response to DON of a double haploid population that segregated for both QTL *Fhb1* and the toxin resistance phenotype (DON induced bleaching). Based on this analysis, they identified genes associated with the DON resistance phenotype at the transcriptional level, including those encoding the aforementioned *TaABCC3.1* ABC transporter, and those coding for cytochrome P450 enzyme homologs (*CYP450*s), an AAA^+ family ATPase, a zinc binding alcohol dehydrogenase-1, a mitochondrial phosphate transporter and an uridine diphosphate-glucosyltransferase (*UGT*). Li et al. (2010) reported that a CYP450 was more highly induced by DON in the FHB and DON resistant wheat cv. Sumai3 than in the susceptible cv. Annong 8455. In a study conducted by Schweiger et al. (2013b), DON induced the transcription of genes encoding UGT and glutathione-S-transferases (GSTs) in wheat carrying both *Fhb1* and a FHB resistance QTL on chromosome 5A (DON independent). In a recent RNAseq study conducted by Hofstad et al. (2016) on wheat near isogenic lines carrying QTL *Fhb1*, DON induced genes included those encoding CYP450s, GSTs, UGTs, an ABC transporter and an O-methyltransferase.

Foroud et al. (2012) analysed the effect of DON, wild type *F. graminearum* and its' DON-minus mutant derivative on the transcriptome of an FHB susceptible wheat genotype and two double haploid lines with moderate FHB resistance derived from the susceptible genotype and resistant parents. The pattern of gene expression in response to DON suggested that the toxin delayed the plant defence response in a susceptible genotype, but was less effective in doing so in the resistant genotypes. DON also up-regulated genes encoding ribosomal components in the resistant wheat lines, but not in the susceptible genotype. The resistant double haploid lines were chosen for the study based on their ability to tolerate DON in an in vitro screen and, as the authors stated, this screen may have selected lines that overproduce ribosome or DON-sensitive ribosome components. Differential expression of phenylalanine ammonia-lyase (PAL) genes was expressed upon DON treatment suggesting the role of phenylpropanoid pathway metabolites in DON response. In the resistant cultivars, the genes coding for PAL are up-regulated and in susceptible cultivars they are down-regulated. Early up-regulation of genes coding for peroxidases and elicitor response PR genes were mainly observed in the resistant lines upon application of DON, suggesting that the resistant lines activate their defence response much earlier than the susceptible lines. Genes encoding terpene synthase, GST, CYP450, GDSL lipase acyl hydrolase and lipoxygenase were activated by the wild type but not by the DON-minus mutant fungus, suggesting they played a role in the response to the toxin.

A study conducted by Boddu et al. (2007) analysed the transcriptional response of barley head tissue to wild type *F. graminearum* and its trichothecene-minus mutant derivative. Although this study was conducted on the FHB susceptible cv. Morex, the comparison of the results obtained for the wild type with those obtained for the DON-minus fungal strain gave insights into the processes activated during barley defence against DON. They found that Contig20755 was responsive to DON production and this is the barley homolog of the wheat DON resistance orphan gene *TaFROG* characterised by Perochon et al. (2015). Other barley genes up-regulated in response to DON production by the fungus encoded UGTs, CYP450s, transporters and proteins involved in ubiquitination and PCD. A subsequent transcriptome study of this barley cv. Morex confirmed that genes encoding ABC transporters, UGTs, CYP450s and GSTs were responsive to pure DON (Gardiner et al. 2010) and that overexpression of cystathionine β-synthase, a key enzyme for glutathione production, enhanced the conversion of DON to the less toxic derivative DON-glutathione in yeast.

Conclusions

Elucidating the host resistance mechanisms that confer resistance to DON and enhance DON detoxification mechanisms will help us to develop tools and strategies to prevent mycotoxin contamination of grain and reduce yield loss due to FHB disease. The information derived from various functional genomics studies gave much insight into the paths to follow in order to enhance DON and thus FHB resistance. Many of the genes identified are expression markers in that they were delineated on the basis of enhanced expression being associated with a toxin resistance phenotype. CYPs, ABC transporters and UGTs are among the most common gene families involved in the cereal response to DON. For some, gene overexpression or gene silencing has confirmed their role in DON resistance; for others, their effect on DON resistance remains to be determined. From a breeding perspective the identification of gene promoter polymorphisms linked to differential gene expression will provide valuable markers for breeders to track specific alleles of interest within their breeding programmes. Genes proven to enhance DON resistance will serve both breeders and the GM industry as tools to develop transgenic, cisgenic or gene-edited crops with enhanced *Fusarium* resistance.

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