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THE REGULATORY MECHANISMS OF WHEAT HEAD SCAB - FUSARIUM GRAMINEARUM; INTERACTIONS, DEVELOPMENT, PATHOGENESIS, DEOXYNIVALENOL (DON) PRODUCTION AND FUNGICIDES SENSITIVITY

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ABSTRACT

Fusarium graminearum causes fusarium head scab or blight disease of cereals. Humid and moist weather conditions facilitate its epidemics leading to a high loss of grain yield and quality. The infected grains are also contaminated with mycotoxins, deoxynivalenol (DON), and nivalenol (NIV), which harm humans and animals. Wheat responds to the initial infection of F. graminearum by enhancing defence mechanisms such as thickened cell walls, dead of the affected tissues and cells, or by limiting the spread of fungal growth in the plant tissue. Farmers have successfully controlled wheat head scab fungus using systemic fungicides, including carbendazim, tebuconazole, phenamacril, and fludioxonil fungicides. Increased occurrence of this disease in the field has led to frequent use of these fungicides, which has resulted in the emergence of fungicide resistance. Understanding the processes involved in the growth, sporulation, virulence, and fungicide sensitivity of F. graminearum are essential for developing effective control measures to combat the infection. This review will focus on the regulatory mechanisms that control wheat-Fusarium graminearum interactions, development, pathogenesis, deoxynivalenol (DON) production, and sensitivity of fungicides.

Keywords: Fusarium graminearum, deoxynivalenol (DON) production, wheat scab- F. graminearum interactions and virulence

1. INTRODUCTION

Fusarium graminearum is an aggressive fungal pathogen that causes Fusarium head scab disease on wheat (Goswami and Kistler, 2004). This pathogen can also affect barley, oat, and many species of cereals and grasses (Schmale and Bergstrom, 2010) by parasitizing their roots, stems, leaves, and reproductive tissues. The infection of wheat tissues can occur through natural openings and direct penetration to the epidermal cells and cuticle (Rittenour and Harris, 2010). Inoculum sources include crop debris, alternate hosts, and infected seedlings (Parry et al., 1995). The pathogen is a filamentous ascomycete, producing both sexual spores and asexual conidia, with the perithecia developing on the mycelia to give rise to ascospores. The ascospores and conidia are dispersed by insect vectors or spore dispersal from infected plants that travel by wind or rain splash onto the floral tissues of the wheat crop (Parry et al., 1995; Rittenour and Harris, 2010). Wheat plants produce stems composed of several spikelets positioned alternatively on the

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spike's stem from which the seed emerges. At an early stage of infection, the ear tissues appear symptomless (Brown et al., 2010), but as the disease develops, spikelets will be bleached, and light pink-colored conidia will appear on the rachis. The spikelets will be glume, while the infected kernels will become rough, shriveled, and changed to light brown, and the grains will shrink and wrinkle. The fungal autogenous hyphae form on the cell surface layers of the infected crop for the perithecial formation and ascospore production at the advanced stage (Parry et al., 1995; Guenther and Trail, 2005; Del Ponte et al., 2007). The disease is prevalent in humid and warm environments, especially during flowering, resulting in *F. graminearum* epidemics and, consequently, significant loss of grain yield and quality reductions (Boyacioğlu and Hettiarachchy, 1995; Brown et al., 2011; Dubey et al., 2017). The infected crop also produces grains contaminated with various mycotoxins, which are detrimental to human and animal health (Kimura et al., 2007; Wu and Munkvold, 2008; Brown et al., 2011).

These mycotoxins include several type B trichothecenes such as deoxynivalenol (DON) and nivalenol (NIV) (Fig 1 and 2), which are the virulence factors that promote the spread of fusarium head scab on the wheat ear (TEKER et al., Proctor et al. 1995a; Proctor et al. 1995b; Guenther and Trail 2005; Brown et al. 2011). The 4-acetyl nivalenol is generated from the NIV chemotype, while 15A- DON and 3A-DON acetylated derivatives are from DON chemotypes and could be found in different geographical regions (Chilaka et al., Ward et al., 2008; Yli-Mattila and Gagkaeva, 2010). There are several types of trichothecenes, including Type A (T-2 toxin and HT-2 toxin), Type B (nivalenol and deoxynivalenol), Type C (crotocin and Type D (macrocyclic: satratoxin H and roridin A) with NIV and DON being the most commonly known (Chen et al., 2019b). These toxins inhibit protein synthesis in the eukaryotic cell by preventing polypeptide chain initiation and elongation through binding with the 60S ribosomal subunit (Kimura et al. 1998; Brown et al. 2011). During the production of trichothecenes, 15 TRI genes encode the enzymes responsible for biosynthesis (Chen et al., 2019b). These genes are the 12 – genes core TRI cluster, two genes at the TRI-TRI16 locus, and the single–gene TRI 101 locus, located at three different loci on different chromosomes in *F. graminearum* (Gale et al., 2005; Alexander et al., 2009). The enzyme; trichodiene synthase is encoded by TRI 5 genes which facilitates the conversion of farnesyl pyrophosphate to trichodiene, the first step in trichothecene production (Brown et al., 2011). Nine reactions sequentially catalyzed by the gene TRI 4, TRI 101, TRI 11, and TRI 3 will then convert trichothecene to calonectrin (Chen et al., 2019b). TRI4 encodes a multifunctional oxygenase needed for trichothecene production by converting trichothecene to isotrichotriol (McCormick et al. 2006; Chen et al,. 2019b). TRI 101gene encodes trichothecene 3-0 acetyltransferase, TRI 11 gene encodes a cytochrome P-450 monooxygenase required for C-15 hydroxylation in trichothecene biosynthesis, and TRI 3 gene encodes 15-O- acetyltransferase sequentially catalyzed the conversion of calonectrin to isotrichotriol (McCormick et al., 1996; Alexander et al., 1998; McCormick et al., 1999). Genetic and genomic studies recently identified novel type A trichothecenes: NX-2 and NX-3 (NX) in *F. graminearum*. The NX trichothecenes were detected to lack a keto group at the C8 position and were also responsible for initial infection and fusarium head blight spread (Hao et al., 2023).

In DON production, the calonectrin is hydroxylated at both the C-7 and C-8 positions by cytochrome P450 monooxygenase TRI and deacetylated by TRI 8 to produce 3-ADON or 15-ADON (McCormick and Alexander 2002; Brown et al. 2003; Chen et al., 2019b) while in NIV production, two alternative pathways can be used; TRI 3 –TRI 7-TRI 1-TRI 8 which uses

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calonectrin as a substrate or TRI 3-TRI 7-TRI 8 which uses the 3,15- acetyl DON as the initial substrate (Chen et al., 2019b),

Some plant defense mechanisms like thickening of the cell wall, production of hydrogen peroxide, and death of affected cells are enhanced in the absence of mycotoxin production at the early phase of wheat ear infection (Jansen et al., 2005; Desmond et al., 2008).

Wheat -*F. graminearum* interaction had two types of plant resistance: Type 1 and Type 11 resistance. Type 1 occurs when wheat plants resist initial infection by *F. graminearum* through the aid of their enhanced plant defense mechanisms, such as thickened cell walls and dead of the affected tissues or cells, while Type 11 resistance is when the wheat plant is resistant to the disease spread (Imboden et al., 2018; Hao et al., 2020). Deoxynivalenol is the major pathogenic factor that stimulates the spread of fusarium head blight in wheat heads; thus, during their biosynthesis, resistant strains of *F. graminearum* are barred from the rachis and could only infect florets, thereby preventing further spread of the disease to the wheat head (BaiG and Desjardins 2001; Jansen et al,. 2005). The wheat plant has been characterized by multiple type 11 resistance quantitative loci (QTLs), including Fhb1, Fhb2, and Fhb7 (Hao et al., 2020; Wang et al., 2020).

The role of plant effectors in plant-pathogen interactions must be considered. Pathogens secret proteins, secondary metabolites, or toxins and are expressed when the pathogens penetrate inside

Some biological control agents produce antagonistic metabolites that inhibit fungal spore germination and kill the membrane and cell walls (Wu et al., 2020). For example, metabolites of *Bacillus subtilis* BS45 were observed to effectively inhibit the growth of *F. graminearum* through oxidation damage and perturbing-related protein synthesis (Lu et al., 2023). *Bacillus* metabolites interact with the cytoplasmic membranes of conidia and interfere with spore *F. graminearum* spores and bud elongation, which resulted in the collapse of the mitochondrial membrane in mycelial cells and the death of the fungi (Han et al., 2015; Zhang and Sun, 2018; Jin et al., 2020; Lu et al., 2023). Similarly, the fungi; Simplicillium *lamellicola* can also be used as a bio control agent to induced resistance against diseases of wheat caused by *F. graminearum* (Abaya et al., 2023). Extracts of Piper sarmentosum have been revealed to possess antifungal activities against *F. graminearum* in wheat (Zhou et al., 2023). In addition, several responses like drought stress, abscisic acid and early ripening drastically reduced fusarium head blight infection in barley (Hoheneder et al., 2023) and thus can also be used to control *F. graminearum* infections.

Synthetic fungicides, however, remain the best way to control wheat head scab fungus, fungicides such as carbendazim, tebuconazole, phenamacril, and fludioxonil have been successfully used by farmers to combat this disease (Zhou and Wang, 2001; Chen and Zhou, 2009; Zheng et al., 2015; Li et al., 2019; Zhou et al., 2020a; Wen et al., 2022). Increased occurrence of this disease in the field resulted in the continuous and frequent use of these fungicides, leading to disease resistance problems (Zhou and Wang, 2001; Chen et al., 2009; Zheng et al., 2015; Li et al., 2017b). Carbendazim binds to β-tubulin, disrupting microtubule formation and mitosis (Davidse and Flach, 1978).

F. graminearum contains two β tubulin isotypes; β 1 tubulin (NCB1 accession number XM_011329885.1) and β 2 tubulin (NCB1 accession number XM_011327927.1) (Chen et al., 2007). A Point mutation in the amino acid sequence at codons 167, 198, and 200 of β 2 tubulin caused *F. graminearum* resistance to carbendazim (Chen et al., 2007). Deletion of β 1 tubulin reduced mycelial growth, spore germination, and pathogenicity of *F. graminearum* but increased its asexual reproduction (Qiu et al., 2012). Furthermore, β1 tubulin deletion mutants displayed

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greater insensitivity to carbendazim fungicide than their wild type; therefore, the β1 tubulin gene rather β 2 tubulin gene is the target for carbendazim in *F. graminearum* (Zhou et al., 2016). Interaction of β2 tubulin genes with isocitrate dehydrogenase 3 (IDH 3) regulates the biosynthesis of deoxynivalenol in *F. graminearum* by decreasing acetyl- CoA accumulation in the fungus (Zhou et al., 2020b). Therefore, reduced interaction between the β2 tubulin genes and isocitrate dehydrogenase 3 result to the acetyl-COA accumulation which stimulates the secondary metabolite deoxynivalenol in *F. graminearum* (Zhou et al., 2016). Fludioxonil interacts with the high osmolarity glycerol (Hog1) cascade of mitogen-activated protein kinase (MAPK) signaling pathway by activating the transport-associated proteins in phosphorylation and glycerol synthesis (Lew, 2010; Yun et al., 2014; Wen et al., 2022). Point mutation of the histidine kinase (HK) OS-1 causes fludioxonil resistance in *F. graminearum* laboratory-resistant strains (Fujimura et al., 2000). Mutations were recently identified in FgOS1, FgOS2, and FgOS4 fludioxonil field resistant strains of *F. graminearum* (Wen et al., 2022). Phenamacril fungicide is essential in binding the myosin-5 motor domain; therefore, the mutation in myosin -5 genes causes *F. graminearum* resistance to phenamacril (Zheng et al., 2015). The deletion of the fourth intron from β 2 tubulin gene, a single intron from CYP 51A, and the second intron from the myosin – 5 genes showed an increase in the sensitivity of their designated fungicides. Understanding the processes involved in the growth, sporulation, virulence, and fungicide sensitivity of *F. graminearum* are vital for developing good control measures to combat the infection. Here, we review the regulatory mechanisms of wheat-*Fusarium graminearum* interactions, fungal development, pathogenesis, deoxynivalenol (DON) production, and fungicides sensitivity.

Briefly, this review covers,

F. graminearum–wheat plant interactions

Mechanisms of *F. graminearum* development, sporulation, virulence, don production, sensitivity to fungicides

2. WHEAT PLANT-*F. GRAMINEARUM* INTERACTIONS

The followings are the wheat plant-*F. graminearum* interactions:

2.1. Coordinated and ordered expression of diverse defense signaling pathways regulate wheat plant - *F. graminearum* interactions

During infection of fusarium head scab disease (Geddes et al., 2008; Li and Yen, 2008; Jia et al., 2009), the genes associated with signaling events are induced. These genes are found to be stimulated by salicylic acid (SA), jasmonic acid (JA), ethylene (ET), Calcium ions (Ca2+), phosphatidic acid (PA), and reactive oxygen species (ROS) production. They are associated with scavenging, antimicrobial compound synthesis, detoxification, and cell wall reinforcement (Ding et al., 2011). The Salicylic acid and calcium ions signaling pathways are initiated within six hours after injection, followed by jasmonic acid-mediated defense signaling activation twelve hours after injection. Ethylene signaling was activated between 6 to 12 hours after injection. Genes for phosphatidic and reactive oxygen species synthesis are mediated during salicylic acid and jasmonic acid phases, respectively. The disruption of the salicylic defense pathway in the mutant increases resistance to *F. graminearum* (Makandar et al., 2006; Ding et al., 2011). Toxins and damage to host cells created by *F. graminearum* may mediate defense mechanisms (Jarosch et al. 2003). Several studies revealed that jasmonic acid and ethylene signaling pathways are important resistance reactions in fusarium head blight infection (Thomma et al., 1998; Geraats et

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al., 2002; Lorenzo et al., 2003; Adie, 2007; Navarro et al., 2008; Pré et al., 2008; Trusov et al., 2009).

The Salicylic and jasmonic/ethylene pathways react negatively in response to resistance (Spoel et al., 2007). The cell wall lignin content is high in fusarium head blight-resistant mutants than in sensitive strains (Kang and Buchenauer, 2000). The mycotoxin DON produced by *F. graminearum* was detoxified by UDP- glucosyltransferase from Arabidopsis thaliana (Poppenberger et al., 2003; Lemmens et al., 2005). The interaction of transcriptome sequencing and heterologous expression in *Saccharomyces cerevisiae* led to the biosynthesis of Cytochrome P450 enzyme, CYP68J5, from *F. graminearum*, which have steroidal 12β- and 15α-hydroxylase activities essential for steroidal drugs production (Wang et al., 2023).

2.2. The role of plant effectors in wheat plant–*F. graminearum* interactions

Pathogens secret proteins, secondary metabolites, or toxins which are expressed as they penetrate inside plant tissue (Hao et al., 2020). In susceptible hosts, biotrophic pathogens secret effectors to reduce the plant defense responses or interact with the cognate-resistant genes to initial cell death, thereby preventing further spread of the pathogen to a resistant host (Friesen et al.. 2007; Hao et al. 2020). *F. graminearum* exhibits both biotrophic and necrotrophic phase of lifestyle in their interaction with wheat host and can secrete up to six hundred effectors (Brown et al.. 2010; Brown et al., 2017). During the biotrophic phase, these effectors can regulate plant immunity and reduce plant defense response but induce cell death to enhance infection and disease spread in the necrotrophic phase (Hao et al., 2020). The effectors are small cysteine-rich proteins (SCPP) that contain N-terminus signal peptides but lack transmembrane domains, and *F. graminearum* possesses about thirty SCPPs which are expressed during their interaction with the wheat plant (Lu and Edwards, 2018). The deletion of FGSG_00569 did not affect the infection of wheat heads by *F. graminearum*, but the resistant strains of FGSG_03112 PR1 –like protein decreased Fusarium head blight spread by 30% (Lu and Edwards, 2018). However, one or triple resistance strains of Kp4- like killer toxin protein such as FGSG_00060, 00061, and 00062 did not affect fusarium head blight spread but caused rot of the seedlings in some wheat varieties (Maluin et al., 2019). Again, some enzymes like lipase-like protein FLG1, Tom 1, and ARB93B secreted by the pathogen have also been indicated to associate with Fusarium head blight disease spread (Voigt et al., 2005; Blümke et al., 2014; Carere et al., 2017; Hao et al., 2019; Hao et al., 2020). *F. graminearum* arabinanase (Arb93B) was also implicated in improving the susceptibility of wheat to head blight disease by reducing reactive oxygen species (ROS) production and suppressing plant immunity (Hao et al., 2019). The expression of many effector-coding genes was upregulated in asymptomatic and symptomatic tissues when *F. graminearum* infects the host plant (Lysøe et al., 2011; Brown et al., 2017). Gene expression experiments showed that three effectors: FGSG_01831, FGSG_03599, and FGSG_12160, secreted by *F. graminearum*, affect plant immunity in wheat head infection, but only FGSG_01831was involved in the initial infection of wheat (Hao et al., 2020). The deletion of FGSG_01831gene significantly suppressed initial infection and deoxynivalenol contamination in wheat, whereas single gene deletion of FGSG_03599 or FGSG_12160 did not affect fusarium head blight disease spread (Hao et al., 2020).

3. MECHANISMS FOR VEGETATIVE GROWTH, SPORULATION, VIRULENCE, DON PRODUCTION, SENSITIVITY OF FUNGICIDES TO *F. GRAMINEARUM*

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3. 1. Physiological role of Pyruvate dehydrogenase kinase (PDK) in *F. graminearum*

Pyruvate dehydrogenase kinase (PDK) is a mitochondrial enzyme that suppresses the production of acetyl –CoA through the selective inhibition of pyruvate dehydrogenase (PDH) activity by phosphorylation (Fig 3) (Schulze and Downward, 2011). Genetic studies revealed that FgPDK1 isolated from *F. graminearum* was essential for conidia formation, fungal growth, stress responses, mycotoxin production, pyruvate dehydrogenase regulation, and pathogenicity (Portillo, 2000; Merhej et al., 2011; Newington et al. 2012; Gao et al., 2016). The deleting FgPDK1 in F. graminearum led to high pyruvate dehydrogenase activity, growth retardation, no perithecia, condition formation, and increased pigmentation. Increased sensitivity to osmotic stress and cell membrane agent was detected in the deleted FgPDK1-resistant strains of *F. graminearum* (Gao et al., 2016). In addition, the accumulation of reactive oxygen species (ROS) and plasma damage is also caused by the deleted FgPDK1-resistant strains of *F. graminearum* (Belozerskaya and Gessler, 2007; Dickinson and Chang, 2011). Consequently, the physiologically deleted mutants blocked the DON production and the virulence of F. graminearum, which reduced the expression of Tri6 (Gao et al., 2016).

3.2. WFhb1-1 role in wheat resistance against fusarium head blight disease

Fusarium head blight disease resistance in wheat is a quantitative trait. Genetic studies on resistance indicated that two or three genes control Type 11 resistance in wheat varieties (Ginkel et al., 1996; Gao et al., 2005). The Wfhb1-1 gene is a functional component of Qfhb1 in the fusarium head blight resistance gene with potential antifungal activity (Paudel et al., 2020). Qfhb1 detoxifies deoxynivalenol accumulation (Lemmens et al., 2005; Hofstad et al., 2016), thickens the secondary cell wall in rachis after infection to prevent spread (Gunnaiah et al., 2012), disrupts pectin methylesterase thereby blocking pathogens from entering the host tissues (Zhuang et al., 2013), regulates jasmonic acid (JA) and ethylene (ET) signaling pathways to elicit local and systemic resistance, inhibits the pathogen or suppress fusarium head blight disease (Gottwald et al., 2012; Xiao et al., 2013; Rawat et al., 2016; Paudel, 2017; Eldakak et al., 2018; Su et al. 2018). Several studies have also identified wheat gene WHhb1-1 as a vital genic component of Qfhb1 in sumac 3 (Li and Yen 2008; Basnet et al., 2012; Zhuang et al., 2013; Paudel et al., 2020).

3.3. Hexokinase genes are essential for deoxynivalenol production and fungal development

Carbendazim resistance in *F. graminearum* might accelerate the biosynthesis of deoxynivalenol in diseased wheat (Zhang et al., 2009). During DON biosynthesis, farnesyl pyrophosphate (FPP) is synthesized by farnesyl pyrophate synthetase in the isoprenoid biosynthetic pathway from geranyl pyrophosphate. The Acetyl- CoA is then generated from the interaction of pyruvate and phosphorylated by hexokinase at the first phase of glycolysis (Cody et al., 2000; Kimura et al., 2007). Two putative genes encoding hexokinase were characterized in *F. graminearum* and were identified to play vital roles in increasing DON production and fungal development (Zhang et al., 2016). The two genes involved in DON biosynthesis in *F. graminearum* were FgHXK1 and FgHXK2. Phylogenetic and comparative analyses showed that FgHXK1 was the prevalent hexokinase gene that positively regulates DON biosynthesis. Deletion of the FgHXK1 mutant gene affects DON production and inhibits vegetative growth and conidiation formation (Zhang et al., 2016).

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3.4. Regulatory roles of introns in fungicide sensitivity to *F. graminearum*

Introns in target genes regulate fungicide sensitivity in *F. graminearum* by influencing the expression of the corresponding dominant genes (Li et al. 2017b). The target genes of benzimidazoles, triazoles, and cyanoacrylates are β 2 tubulins, CYP 51 A, and myosin -5, respectively (Chen and Zhou 2009; Liu et al. 2011; Zheng et al. 2015). Mutation of β 2 tubulin gene rather β 1 tubulin gene cause resistance of *F. graminearum* to carbendazim (Chen et al., 2009). The deletion of β2 tubulin mutant significantly increased the sensitivity of *F. graminearum* to carbendazim (Li et al., 2017b). β 2 tubulin gene decreased mycelial growth rate, conidia formation, and pathogenicity in *F. graminearum* (Qiu et al. 2011; Li et al. 2017b; Li et al. 2019). Tebuconazole and triadimefon suppressed the biosynthesis of ergosterol in *F. graminearum* through their sterol 14a-demethylase (CYP51) binding, thus used to control fusarium head blight disease (Liu et al. 2011; Zhao et al. 2022). In addition, *F. graminearum* had three paralogous CYP51 genes: CYP51A, CYP 51B, and CYP 51C. The deletion of CYP 51A mutants significantly increased the sensitivity of *F. graminearum* to demethylation inhibitors by decreasing the formation of conidia (Liu et al., 2011; Chen et al., 2015). Consequently, phenamacril fungicide is essential in binding the myosin-5 motor domain; therefore, the mutation in myosin -5 genes causes *F. graminearum* resistance to phenamacril (Zheng et al., 2015). The deletion of the fourth intron from β 2tubulin, the sole intron from CYP 51A, and the second intron from the myosin – 5 genes indicated an increase in the sensitivity of their designated fungicides. Contrarily, deleting the first or second intron of β 2tubulin gene increased resistance to carbendazim (Li et al., 2017b; Li et al., 2019).

3.5. The G443S Substitution of the Drug Target FgCYP51A gene regulates *F. graminearum* resistance to Ergosterol biosynthesis inhibitors (EBI)

The homologous replacement study demonstrated that G443S substitution of FgCYP51A regulates ergosterol and DON biosynthesis in *F. graminearum*-resistant populations (Zhao et al. 2022) by increasing EBI fungicides resistance to *F. graminearum* mutants. Deletion of ergosterol mutant significantly decreased biological functions of the cell membrane and fungal growth (Ruge et al., 2005). The enzyme responsible for sterol biosynthesis is the cytochrome P450 sterol 14α-demethylase encoded by CYP51, and it is the main target of EBIs. The mutations in CYP51 genes, overexpression of the CYP51 A1 gene, and the overexpression of ATP-binding cassette transporter decreased binding of the target protein with the EBIs, increased ergosterol biosynthesis inhibitors fungicides resistance, and improved efflux pumps which reduced the deposition of fungicides in fungi (Lee et al., 2001; Zwiers et al., 2002; Reimann and Deising, 2005; Cools et al., 2012; Villani et al., 2016). Mutation of the CYP 51 A gene is the primary mechanism of resistance of EBIs to *F. graminearum* (Zhao et al., 2022). Therefore, FgCYP51A-G443S substitution (GGT →AGT, G443S) increases spore formation, DON production, and EBI fungicide resistance but decreases virulence and perithecium capacity of *F. graminearum* mutants (Zhao et al., 2022).

3.6. The regulatory role of FgMad 2 and FgBub 1 in *F. graminearum*

The spindle assembly checkpoint (SAC) governs the attachment of chromosomes to spindle microtubules in mitosis and meiosis (Musacchio and Salmon, 2007). Signal assembly checkpoint genes; Mad 2 and Bub1 affect fungal development and fungicide resistance to *F. graminearum* (Zhang et al., 2015). These genes disrupt anaphase-promoting complex or cyclo-some (APC/C),

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thereby creating time for the correction of errors in chromosome attachment (Gardner and Burke, 2000). The deletion of Mad 2 inhibits meiosis and mitosis, thus increasing the sensitivity of *F. graminearum* to benomyl (Chen et al., 1999). In contrast, the deletion of Bub1 did not disrupt the signal assembly checkpoint and thus is essential in mitosis regulation (Johnson et al., 2004). The FgMad 2 deletion mutants decreased radial growth rate, aerial mycelia, conidia formation, and pathogenicity (Goswami and Kistler, 2004). Therefore, FgMad2 and FgBub genes decrease fungal development, pathogenicity, and *F. graminearum* resistance to carbendazim (Zhang et al., 2015).

3.7. Phenylalanine in position 240 of Fgβ2- tubulin regulates *F. graminearum* sensitivity and resistance to carbendazim

Carbendazim fungicide is one of the benzimidazoles that inhibit pathogen β-tubulins through their selective binding affinity to β-tubulin subunits of the α/β- heterodimer (Davidse, 1986). Plant pathogenic fungi differ in response to sensitivity in carbendazim due to their differences in β-tubulin sequence (Davidse, 1986; Hongxia et al., 2002; Chen et al., 2009; Zhu et al., 2018). The differences in position 240 of β- tubulin regulate the sensitivity and resistance of *F. graminearum* and other phytopathogenic fungi. The phenylalanine in position 240 of Fgβ2-tubulin of *F. graminearum* causes its resistance to carbendazim (Zhu et al., 2018), whereas position 240 in β- tubulin of *Botrytis cinerea*, *Colletotrichum gloesporioides*, and *Sclerotinia sclerotium* is leucine. Two β-tubulin subunits: Fgβ1 and Fgβ2, are possed by *F. graminearum*, unlike other plant pathogenic fungi (Zhou et al., 2016), position 240 is leucine in Fgβ1-tubulin while phenylalanine is in position 240 of Fgβ2 –tubulin. However, Fgβ1 tubulin is considered to be the binding target of carbendazim in *F. graminearum* rather than Fgβ2, thus giving the reason why mutations were found in Fgβ2 –tubulin gene in carbendazim-resistant field isolates of *F. graminearum* (Chen et al., 2007; Chen et al., 2009; Qiu et al., 2011; Wen et al., 2022). Therefore, differences in position 240 of β-tubulin confer the differences in the sensitivity of different plant pathogenic fungi to carbendazim (Zhu et al., 2018).

3.8. Glucose-6-phosphate Isomerase FgGP1 of β2 tubulin gene governs fungal development and deoxynivalenol production in *F. graminearum*

Carbendazim resistance isolates of *F. graminearum* induced pyruvate and acetyl-coenzyme (CoA) biosynthesis (Zhou et al., 2020b). Pyruvate is important in synthesizing several secondary metabolites, including deoxynivalenol, penicillin, and aflatoxin, which are mediated by glycolysis (Kimura et al., 2007). Glucose- 6-phosphate isomerase (GPI) is an enzyme that synthesizes the second phase of glycolysis and catalyzes the reversible isomerization of glucose -6-phosphate and fructose -6-phosphate (Lin et al., 2009; Haller et al., 2011). The biological and genetic studies by (Zhou et al., 2021b) showed that deletion mutants of FgGP1 significantly suppressed mycelia growth, conidia, and septa formation of *F. graminearum*. In addition, FgGP1 is critical for glucose metabolism, ATP biosynthesis, and common carbon utilization, thus decreasing pyruvate production, deoxynivalenol biosynthesis, and pathogenicity in F. graminearum (Zhou et al., 2021b).

3.9. Functional roles of different tubulins (β1, β2, α1, and α2) in vegetative growth, conidiation, and pathogenicity of *F. graminearum*

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F. graminearum have four different α-/β tubulin heterodimers, namely: β1, β2, α1 and α2 tubulin (Zhao et al., 2014). The tubulin: α 1-β 1, α 1-β 2, α 2-β 1, and α 2-β 2 are joined together to form a single microtubule, α 1-, α 2- tubulins can be functionally interchangeable in microtubule assembly, vegetative growth, and sexual reproduction (Zhu et al., 2021). Earlier studies on microtubules assembly showed that the deletion of α-1, α- 2, β-1, and β-2 tubulin mutant genes exhibited changes in their growth rate, conidia formation, virulence, and sensitivity to carbendazim fungicide (Qiu et al., 2012; Hu et al., 2015; Zhao et al., 2017; Zhu et al., 2018). Deletion of β1 or β2 tubulin mutant genes did not affect the microtubule assembly (Wang et al., 2019). Notwithstanding, the deletion mutants of β1, β2, α1, and α2 play a vital role in DON biosynthesis in *F.graminearum* (Zhou et al., 2021a).

3.10. S-adenosyl-L-homocysteine hydrolase FgSah regulates fungal development and virulence in *F. graminearum*

S-adenosyl-L-homocysteine hydrolase (Sah 1) is a gene belonging to NAD (P)/NAD (P) +binding proteins with Rossmann-fold (Rao and Rossmann, 1973), a well-conserved yeast protein generated from the homologous amino acid sequence between human and yeast orthologs (Mushegian et al., 1998). Mutation of Sah 1 results to S-adenosyl-L- homocysteine (AdoHcy) biosynthesis and virulence of pathogens (Shi et al., 2021b). When Sah hydrolyses AdoHcy to homocysteine (Hcy), methionine is liberated, and the process is catalyzed by the enzyme methionine synthase (Met6) (Reed et al., 2004; Tehlivets et al., 2013). The presence of FgSah1 in F. graminearum plays an integral role in the pathogenicity, methylation metabolism, sporulation, conidiation, stress response, DON biosynthesis, and lipid metabolism (Shi et al., 2021b). Methionine is converted to S-adenosyl-L-methionine (AdoMet) by methionine adenosyltransferase, S-adenosyl –L- methionine then changes to S-adenosyl-L-homocysteine (AdoHcy) with the deletion of the methyl group (Fig 4). AdoHcy, which is a by-product of methylation, is hydrolyzed to homocysteine (Hcy) by Sah 1, while methionine is regenerated from Hcy by methionine synthase (Met6) (Liu et al., 1992; Reed et al. 2004; Tehlivets et al., 2013). Deletion of FgSah1 mutants reduced the growth rate but increased the accumulation of acetyl- CoA (Frandsen et al., 2006; Duan et al., 2020; Zhou et al., 2020b). FgSah 1 is also involved in glycerol production and lipid metabolism in *F. graminearum*; thus high osmolarity glycerol (HOG) pathway governs the glycerol content of *F. graminearum* by mitogen-activated protein kinase (MAPK) Hog1 phosphorylation to maintain homeostasis (Burg et al., 1996). Decreased glycerol biosynthesis in FgSah1 mutants of *F. graminearum* increased the sensitivity of osmotic pressure fungicides, fludioxonil, and iprodione (Rangel et al., 2015).

3.11. The two l-lactate dehydrogenases, FgldhL1 and FgldhL2, are involved in *F. graminearum* development and virulence

Lactate dehydrogenase is in two groups: Group 1 includes l-lactate ferricytochrome c oxidoreductase (L-LCR) (Bernheim, 1928) and NAD-dependent l-lactate dehydrogenase (Wang et al., 2014), while groups 11 are the d-lactate ferricytochrome c oxide-reductase (D-LCR) (Nygaard 1960), d-lactate dehydrogenase (D-LDH) and NAD-dependent d-lactate dehydrogenase (Genga et al., 1983). Lactate dehydrogenase plays a vital role in the fungal energy metabolism from glycogen and lipid droplets reserved in spores (Chen et al., 2019a). Lactate regulates cellular homeostasis (Brooks 2002) and transports l-lactate metabolism in human hepatocellular carcinoma G2 cell mitochondria (Pizzuto et al., 2012). The conversion of

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pyruvate to lactate in the peroxisome is by the oxidation of NADH to NAD+, which regulates cellular redox homeostasis for the healthy cycles of β- oxidation in peroxisomes and glycolysis in the cytosol (Zhou et al., 2017; Chen et al., 2019a). FgldhL1 and FgldhL2 in *F. graminearum* are major intermediate enzymes that are involved in the metabolism of energy reserved in the spores or ascospores, deletion of FgldhL1 and FgldhL2 mutants reduced sporulation, spore germination, carbon source utilization, DON production, and virulence (Chen et al., 2019a).

3.12. The transcription factor FgNsf1 is essential for fungal growth, virulence, and stress responses in *F. graminearum*

Cys2-His2(C2H2) zinc finger is an important DNA-binding motif found in eukaryotic transcription factors characterized in transcription factor 111a (TF111a) isolated from Xenopus laevis with tandem repeats of about 30 amino acids motifs (Brown et al. 1985; Miller et al. 1985; Wolfe et al. 2000) while zinc finger is a small structural protein motif that is made up of zinc ions in folds (Jantz et al. 2004; Michalek et al. 2011; Maret 2012; Lee and Michel 2014).

Nutrient stress factor 1 (Nsf1) is the C2H2 zinc finger protein of *F. graminearum* (Son et al., 2011). Deletion of the FgNsf1mutant gene decreases vegetative growth, sporulation, and conidia formation but increases pigmentation, osmotic stress, cell wall damaging agents, and oxidation stress in *F. graminearum* (SHI et al., 2021a). In addition, FgNsf1 deletion mutants increased *F. graminearum* sensitivity to carbendazim, tebuconazole, fludioxonil, and iprodione fungicides, thus reducing virulence and DON production. The gene FgNsf1, therefore, is essential for vegetative growth, sporulation, conidia formation, stress response, fungicide sensitivity, and virulence in *F. graminearum* (SHI et al., 2021a).

3.13. Sey1/atlastin, a dynamin protein, is critical for fungal development, pathogenicity, and DON production in *F. graminearum*

The mycotoxin; deoxynivalenol (DON) produced by fusarium head blight fungus is mediated in the endoplasmic reticulum (ER). Several plant physiological processes, including protein translocation, modification, lipid production, and regulation of intracellular calcium homeostasis, are carried out in the endoplasmic reticulum besides DON production (Daumke and Praefcke 2011; Klemm et al., 2013; Hu and Rapoport 2016; Sugiura and Mima 2016; Li et al., 2017a). Sey1/atlastin is a dynamin-like protein in the endoplasmic reticulum, which initiates homotypic fusions among the membranes (Chong et al., 2020). The absence of Sey1 in the endoplasmic reticulum caused delayed fusion of the membranes (Anwar et al., 2012; Yan et al., 2015). Sey1 also initiates nuclear fusion during mating in yeast (Kanfer et al., 2017, and regulates the size of lipid droplets (LDs), neuronal defects in mammalian cells, and drosophila (Summerville et al. 2016). The deletion mutant of FgSEY1 significantly decreased vegetative growth, conidial formation, DON production, and pathogenicity of *F. graminearum*, thus critical for hyphal growth, asexual reproduction, virulence, and DON biosynthesis (Chong et al., 2020).

3.14 Fg AP1$^{\sigma}$ roles in *F. graminearum* vegetative growth, conidia formation, pathogenicity, and DON production

Clathrin adaptor protein (Aps) is one of the structural components of clathrin transport vesicles which are essential in vesicle assembly, recruitment of membranes cargoes and coat proteins, and vesicular transport (Ohno, 2006; Popoya et al., 2013; Wu et al., 2023). Fungi have three functional AP complexes: AP1, AP2, and AP3 and of; which AP1 complex is the most

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conserved heterotetrameric protein complex that binds membranes rich in phosphatidylinositol 4-phosphate, such as the membrane of the trans-Golgi network (TGN) and regulates cargo sorting between trans-Golgi network (TGN) and recycling endosomes (Robinson, 2004; Li et al., 2016; Martzoukou et al., 2017; Beacham et al., 2019). The AP1 complex consists of two large (~ 100 kDa) subunits, beta-adaptin (β) and gamma-adaptin (Y), one medium-sized (~ 50 kDa) subunit (μ), and one small (~ kDa) subunit sigma (σ) (Wu et al., 2023). FgAP1σ regulates the development, cell wall integrity, responses to osmotic stress, DON production, pathogenicity, and transportation of vesicles in *F. graminearum* (Wu et al., 2023). The disruption of FgAP1σ negatively affects fungal vegetative growth, conidia formation, spore production, virulence, and DON production (Wu et al., 2023). The well-conserved FgAP2 complex subunits FgAP2β, FgAP2σ, and FgAP2mu regulate the growth, development, and virulence of *F. graminearum* (Zhang et al., 2019).

4. CONCLUSION

Fusarium head blight is a devastating fungal disease of wheat, barley oats, and cereal crops. This disease causes loss of grain yield and quality and produces myotoxins, including deoxynivalenol and nivalenol, which are harmful to humans and animals. Most wheat varieties are susceptible to *F. graminearum* infection; thus, control has been mainly through systemic fungicides. However, continuous and extensive use of these fungicides resulted in the fungus developing resistance to the chemical, leading to crop failure and poor crop yield. Understanding the mechanisms involved in the growth, sporulation, virulence, and fungicide sensitivity of *F. graminearum* is vital for developing good control measures. Such knowledge also stimulates the development of novel and innovative strategies for preventing and treating its resistance problems, early detection, monitoring, and plant disease management.

CONFLICT OF INTEREST

This manuscript has no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Chang-jun Chen: Conceptualization, Supervision, AUTHORSHIP CONTRIBUTIONS
Chang-jun Chen: Conceptualization, Supervision, JI: Writing the original manuscript draft, DS: writing the original manuscript draft. All authors edited, reviewed, and approved.

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FIGURES

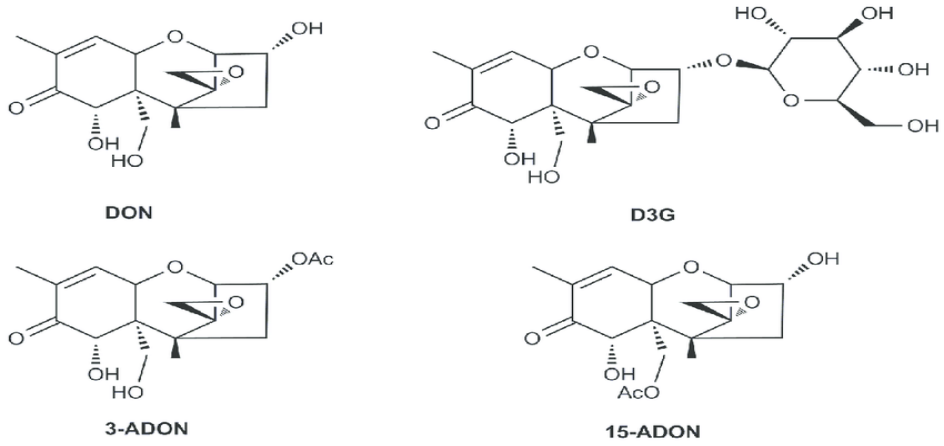

FIgure 1-Chemical-structures-of-deoxynivalenol-DON-deoxynivalenol-3-glucoside-D3G

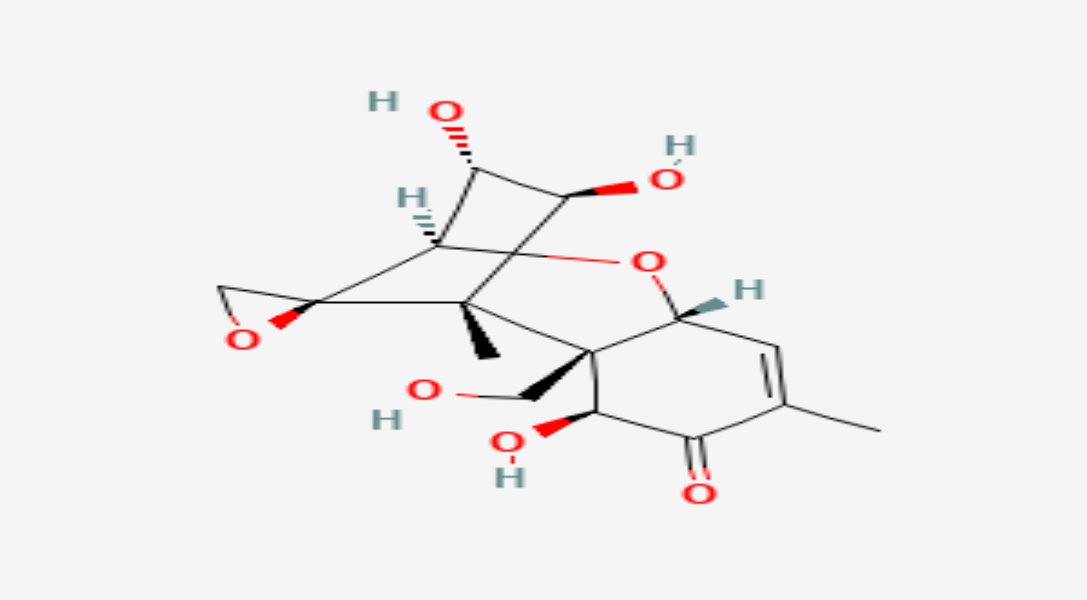

Figure 2- Chemical structure of nivalenol (NIV)

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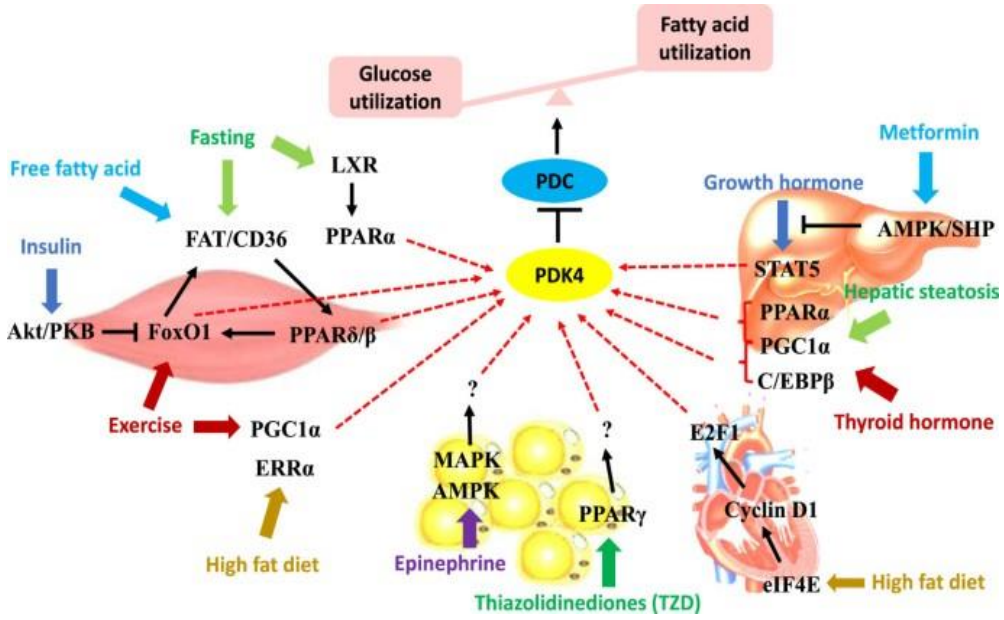

Figure 3- Physiological role of Pyruvate dehydrogenase kinase (PDK) in *F. graminearum*

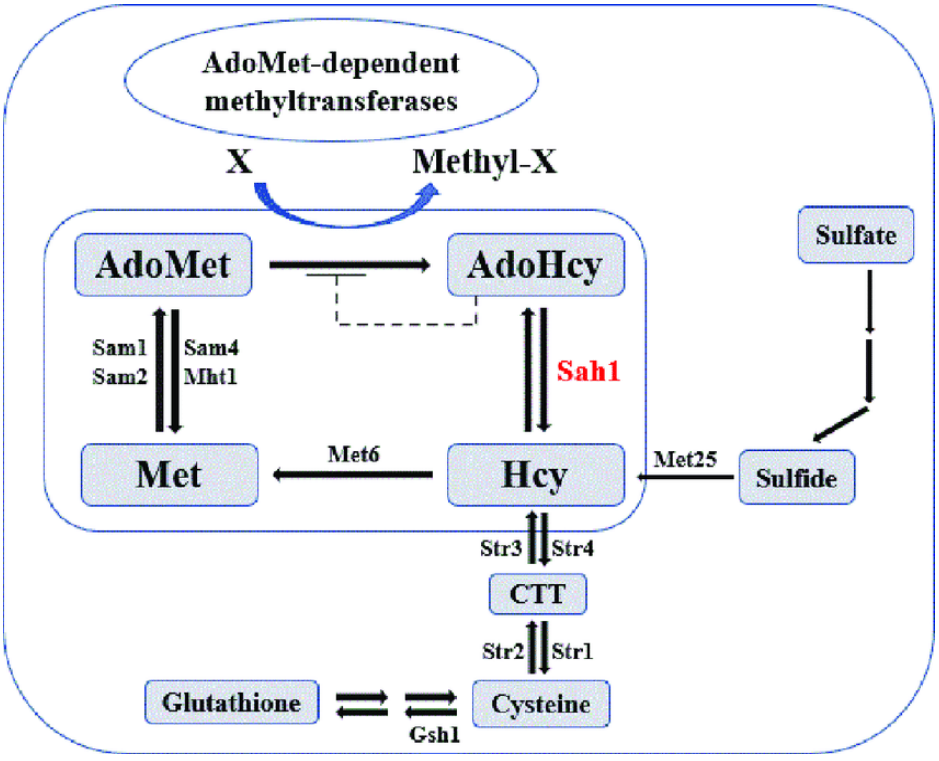

Figure4-Model-of-the-methionine-cycle-in-yeast-Sah1-is-marked-in-a-red-font