Fusarium graminearum

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Fusarium graminearum, the main causal agent of Fusarium Head Blight (FHB), is one of the most damaging pathogens in wheat. Because of the complex organization of wheat resistance to FHB, this pathosystem represents a relevant model to elucidate the molecular mechanisms underlying plant susceptibility and to identify their main drivers, the pathogen's effectors.

Fusarium graminearum | Triticum aestivum | plant–fungus interaction

1. Introduction

Fusarium Head Blight (FHB), mainly caused by the Ascomycota fungus *Fusarium graminearum*, is one of the most prevalent diseases of small grain cereals, especially in wheat [1][2]. With direct impacts on yield, grain quality and through the accumulation of carcinogenic mycotoxins (e.g., deoxynivalenol, DON) [3][4][5], FHB is considered as a major limiting factor for wheat production in Europe, North America and Asia [6][7][8][9], resulting in substantial economic losses that reached up to USD 1.176 billion over 2015 and 2016 in the USA for instance [10]. Because FHB is expected to be even more frequent and intense along with the rises of temperatures and the occasional increases in air humidity promoted through the climate change [11][12], further research is needed to develop better management strategies and sustainable control solutions [13]. FHB resistance trait is strictly quantitative and involves multiple Quantitative Trait Loci (QTLs) with relatively weak effects [14][15] that makes them insufficient when environmental conditions are favorable to the fungus. Thus, identifying sustainable solutions able to efficiently control FHB epidemics requires the search of alternative sources of resistance. For the last twenty years, the multiple evidences of the role of a plant's susceptibility factors in promoting pathogen infection have opened new opportunities to identify such pivotal determinants of plant diseases, and a number of studies already reported that mutation or loss of susceptibility genes can be used in resistance breeding [16][17]. With the increasing evidences of the role of wheat's susceptibility factors in FHB development [18][19][20][21][22][23], elucidating the mechanisms of wheat susceptibility to *F. graminearum* appears as a promising approach to improve FHB resistance [17][24][25][26].

A pathogen's ability to hijack a host's biological processes such as defense responses, physiology and primary metabolism to exploit host resources is assumed to be one of the key drivers of a plant's susceptibility. These interactions involve a complex molecular crosstalk between the two partners, including the delivery of effectors, which include small secreted proteins able to alter host cell structure and to target specific functions into host tissues, the so-called susceptibility factors [27][28][29][30][31][32]. The role of an effector is therefore determined by its in planta localization, i.e., the apoplast or host's intracellular compartments, and the targeted susceptibility factors [32][33][34][35]. Mining a robust catalog of pathogen effectors, i.e., the effectome, offers major opportunities to improve

resistance breeding through the identification of the host's susceptibility factors, i.e., the targetome. This further could make possible the identification of functional markers to screen plant germplasm, as well as new targets for host-induced gene silencing [32][36][37]. However, their systematic search in silico is still challenging because most of them lack shared protein features or conserved domains within and across species, and very few are structurally characterized [28][32][35]. The only universal fungal effector's characteristics are their expected secretion and their fine-tuned synthesis along the infection progress [35][38], making in planta exploratory methods such as transcriptomics and proteomics necessary to narrow down the effector candidates and identify the active ones [37][39][40].

Numerous effectors are deployed by pathogens and their role within the molecular crosstalk and in the fate of the interaction is determined by their conservation among pathogen species or between the different strains of a particular species. This conservation is also partly driven by the coevolution with their hosts and their targetome [40][41]. Conserved effectors are thought to play an indispensable role to ensure compatibility by targeting conserved host's immune or metabolism functions, while specific effectors are thought to be involved in the host's adaptation and strain aggressiveness [40][41][42][43]. Thus, elucidating the complexity of such molecular crosstalk underlying plant–pathogen interactions and elaborating robust and relevant effectomes require consideration of the diversity from both partners of the interaction. The genomics variability of many fungal pathogen species is well characterized, but its impacts on the infection program remains to be addressed [44][45][46][47][48].

In *Fusarium graminearum*, genomics variability has been well characterized and the first pangenome of the species, built from 20 strains, was published in 2021 [49]. If the in silico characterization of *F. graminearum* secretome [49][50] is now available, our knowledge about the effective in planta effectome remains fragmented and needs to be clarified. Several in planta studies outlined a highly dynamic and complex molecular dialogue between wheat and *F. graminearum*, involving a stage-specific delivery of the effectors [19][25][51][52]. However, the impacts of wheat and *F. graminearum* genetic backgrounds are largely unknown. In a previous proteomics study, *F. graminearum* infection strategy was described in three strains of contrasting aggressiveness facing three wheat cultivars of contrasting susceptibility at one time point, resulting in the identification of highly conserved fungal determinants of the infection [20]. Owing to its higher ability in detecting low-abundant molecules, as are the fungal molecules within host tissues, applying RNA-seq technology over infection progress appears as a promising approach to complete the picture of *F. graminearum* effectome during FHB and to identify its core components.

2. *Fusarium graminearum* Infection Involves a Highly Conserved Effectome

Transcriptome profiling of effector coding genes conducted on the three *F. graminearum* strains of contrasting aggressiveness and on the five hosts of contrasting susceptibility to FHB revealed highly conserved effector repertoires. We demonstrated that the three strains shared 90% of their effector-gene transcripts. While at the genomic scale, these three strains shared only 58% of their theoretical secretome [49], our results corroborate a previous in planta proteomics study demonstrating that nearly 100% of the whole identified secreted proteins were accumulated in the same three strains [20]. This emphasizes that the effective infection process of the three strains

on wheat is based on a conserved effectome that controls critical plant processes to ensure the success of the infection. Similar results were already found in other pathosystems. For instance, the gene expression analysis of six *Puccinia triticina* strains highlighted a highly conserved infection strategy with 85.7% of the identified secretome genes expressed by all the strains during wheat infection [44]. Similar findings were also reported in the maize–*Exserohilum turcicum* interaction where 97% of the putative effector genes were shared by two strains [48]. Extending this analysis to the role of host genetic background on the expressed effectome, our data also demonstrated a highly conserved infection strategy in different wheat cultivars of contrasting susceptibility to FHB that engages a common effector repertoire shared at 91%. Few hosts' specific gene expressions were already outlined at the whole-transcriptome scale [53]. Our results support similar conclusions with a special focus on the effectome gene set and are consistent with our previous proteomics study demonstrating the accumulation of the same fungal proteins in different wheat hosts [20]. A core effectome composed of 357 genes expressed by all the strains and in all wheat hosts (**Figure 1**) exemplified the highly conserved infection program established by *F. graminearum.* Because the interaction is systematically producing FHB disease regardless of the strain aggressiveness or the host susceptibility, these genes likely include key drivers of FHB in bread wheat. Their functions are thus supposed to be crucial determinants of basal processes powering the FHB development in wheat, including 66 putative effector genes and 21 Phi-base matches known to be involved in pathogenicity.

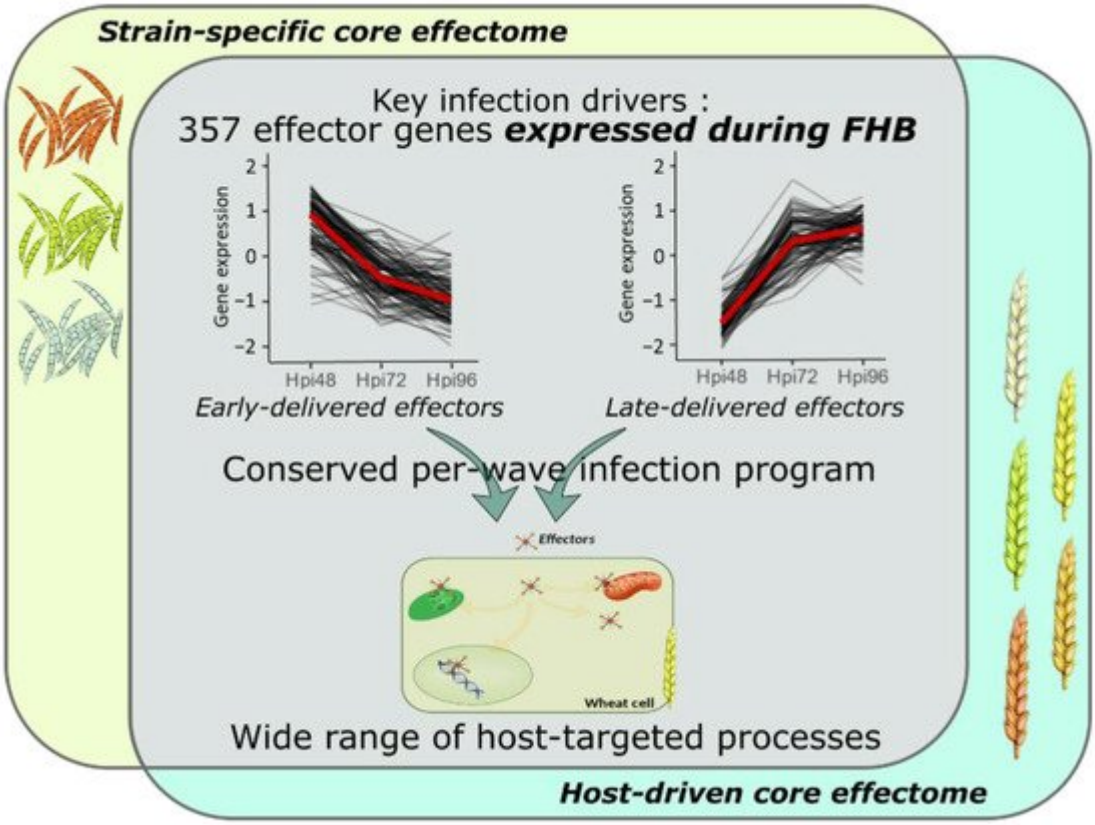

Figure 1. Model summarizing the conserved and complex *F. graminearum* infection strategy on wheat spikes. As a whole, 357 effector genes were identified as the key drivers of FHB infection expressed by all the strains and in all the infected hosts; they represent the *F. graminearum* core effectome. These genes were expressed at very specific infection stages in a per-wave manner, including genes highly expressed at the very beginning of the

interaction with the wheat tissues and others highly expressed in the later stages of the infection. The timing of gene expression was mostly conserved independently of the strain or the host. Targeted processes within the host are highly diverse with a wide array of targeted compartments and predicted functions.

3. *F. graminearum* Core Effectors Are Delivered in a Conservative Per-Wave Expression

The core-effectome demonstrated to be deeply remodeled along with the infection progress, depicting the dynamic nature of its components. As previously shown, putative effector proteins were proved to be accumulated at specific stages of the infection process evidencing a specific transition that distinguishes early from late protein accumulations [19]. In line with this previous work, we also observed changing gene expression patterns at the same time (48 to 72 hpi transition), thus corroborating the major reorganization of the molecular arsenal that drives FHB infection. Furthermore, the fine-tuned timing of gene expression was mostly preserved in terms of dynamics for all the strains independently of their aggressiveness and in all the infected hosts independently of their susceptibility level, suggesting that *F. graminearum* set up a widely conserved genetic program with crucial functions required at very precise infection stages (**Figure 1**). This conserved infection program may be representative of *F. graminearum* generalist lifestyle, i.e., interacting with a wide range of hosts and spreading in different tissues [2][54], which results in a lower selection pressure and coevolution with a specific host species [43][55][56].

Besides these conserved infection patterns, some specific regulations in effector-genes were also found in the different fungal strains, but no clear link between gene expression magnitude and aggressiveness has been observed. Identified effector-genes were mainly located in the fast-evolving part of *F. graminearum* genome, characterized by genes of shorter size, larger variations in exon content and a higher proportion of synonymous and nonsynonymous mutations, together with genes known to be highly transcribed during plant infection in comparison with fungal vegetative growth [49][57][58]. In our study, chromosome 2 for instance, displaying the highest density of polymorphism, also exhibited the highest effector gene density [57]. This polymorphism could explain a part of the observed strain-specific effects on effector-genes expression levels and further protein accumulations. Moreover, intrinsic characteristics of both MDC_Fg1, i.e., a French isolate [59], and ‘Chinese Spring’, i.e., an Asian spring cultivar, might be the main cause of *F. graminearum* specific expression patterns of the late-delivered effectors observed when facing ‘Chinese Spring’ in comparison to the European winter wheat cultivars, suggesting a remarkable ability to adapt to the different molecular contexts expressed in different wheat cultivars.

4. *F. graminearum* Infection Strategy Involves Integrative Host Cellular Processes

The search for localization signals within the *F. graminearum* secreted protein sequences revealed that putative effectors can target host apoplast, as well as different subcellular compartments including nucleus, chloroplast and mitochondria at several infection stages (**Figure 7**). Along with the relatively high diversity of predicted functions

(66 GO terms and 140 Pfam), this supports that the infection success is based on a wide array of manipulated host pathways and echoes previous studies that evidenced the diverse nature of processes involved in FHB susceptibility [19][20][23].

Host apoplast appeared as the main target of the *F. graminearum* core effectome, including 53 putative genes with additional effector features, i.e., small cysteine-rich proteins. These genes gathered 65 CAZymes that depict the role of cell-wall degradation during FHB to promote host colonization and nutrient acquisition [60]. Eighteen others belonged to peptidases suggesting that *F. graminearum* is able to override host defense mechanisms especially by interacting with chitin and glucan-triggered immunity and inhibiting host enzymes and proteases as well as to acquire nutrients [61][62][63][64]. Besides these proteases, a guanine-specific ribonuclease was also predicted as a core apoplastic putative effector extending the control of plant stress responses to secreted nucleotidases [60][65]. In addition, three killer toxin KP4-like genes were also identified. Although a previous work has already shown their upregulation during wheat seedling rot disease and FHB, their role in virulence was proved only in seedling rot disease [66].

Intracellular core effectors of *F. graminearum* mainly targeted host nucleus, including two that match with validated virulence factors, a cysteine-rich secretory protein [67] and a PhoD-like phosphatase protein [68][69] along with one gene with additional effector features, i.e., a small cysteine rich protein. Through its eight predicted core nuclear proteases, *F. graminearum* might reprogram host gene expression by interfering with the plant's transcription factors. This strategy was already found in the pathogenic bacteria *Xanthomonas euvesicatoria* and *Pseudomonas syringae* that target transcription factors involved in phytohormone pathways [70][71]. Nuclear effectors are also known to act on host transcription machinery by a direct binding on DNA, such as the *Melampsora larici-populina* Mlp124478 effector that represses genes involved in defense mechanisms [72]. A same strategy might be involved in the *F. graminearum* infection process though its own nuclear effectors.

Chloroplast and mitochondria were also important targets of *F. graminearum* core effectome, including three and one genes encoding small cysteine rich proteins, respectively, as well as a putative mitochondrial PhoD-like phosphatase virulence factor [68][69]. These organelles represent important biological hubs interconnecting primary metabolism, energy production, signaling pathways and plant responses to stress [73][74]. The inhibition of the defense mechanisms through the manipulation of chloroplast [75] and mitochondrial [76] processes was already evidenced in several plant–fungi interactions and proved here to be part of the *F. graminearum* infection strategy. In the case of the chloroplast, its central role has already been described in previous FHB studies [19][20][23]. Finally, effectors with multiple host targets were also detected, suggesting that one effector can achieve completely different functions during the infection progress. An effector targeting both the chloroplast and the mitochondria was validated in poplar—*Melampsora larici-populina* [77][78] and, as it was outlined in *Blumeria graminis f. sp. hordei* with the BEC1054 RNase-like effector, those versatile effectors seem to disturb one specific process, such as a host's defense mechanisms, at several levels by interacting with multiple host proteins [79].

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