

1 **Research Article | LARGE-SCALE BIOLOGY**

2 **Metatranscriptomic comparison of endophytic and pathogenic *Fusarium*–*Arabidopsis***
3 **interactions reveals plant transcriptional plasticity**

4

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24 **Short title: *Arabidopsis*–*Fusarium* metatranscriptomics**

25 **One-sentence summary:** Multiomics analysis reveals the regulatory plasticity of plants in
26 response to beneficial and antagonistic microbes, resulting in distinct phenotypes and rewired
27 transcriptional networks.

28

29 **ABSTRACT**

30 Plants are continuously exposed to beneficial and pathogenic microbes, but how plants recognize
31 and respond to friends versus foes remains poorly understood. Here, we compared the molecular
32 response of *Arabidopsis thaliana* independently challenged with a *Fusarium oxysporum*
33 endophyte Fo47 versus a pathogen Fo5176. These two *Fusarium oxysporum* strains share a core
34 genome of about 46 Mb, in addition to unique 1,229 and 5,415 accessory genes.
35 Metatranscriptomic data reveal a shared pattern of expression for most plant genes (~80%) in
36 responding to both fungal inoculums at all time points from 12 to 96 h post inoculation (HPI).
37 However, the distinct responding genes depict transcriptional plasticity, as the pathogenic
38 interaction activates plant stress responses and suppresses plant growth/development related
39 functions, while the endophytic interaction attenuates host immunity but activates plant nitrogen
40 assimilation. The differences in reprogramming of the plant transcriptome are most obvious in 12
41 HPI, the earliest time point sampled and are linked to accessory genes in both fungal genomes.
42 Collectively, our results indicate that the *A. thaliana* and *F. oxysporum* interaction displays both
43 transcriptome conservation and plasticity in the early stages of infection, providing insights into
44 the fine-tuning of gene regulation underlying plant differential responses to fungal endophytes
45 and pathogens.

46

47 **Keywords:** *Arabidopsis thaliana*, comparative genomics, endophyte, *Fusarium oxysporum*,
48 host–fungal interactions, pathogen

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50

51 **INTRODUCTION**

52 Over millions of years of coevolution, plants and microbes have established intimate
53 relationships, forming beneficial, neutral, or antagonistic partnerships. Plant pathogens threaten
54 agricultural production and global food security (Dean et al., 2012; Strange and Scott, 2005), but
55 beneficial microbes, such as rhizobia, mycorrhizae, and endophytes limit plant pests and promote
56 plant growth through nutrient mineralization and availability (Rashid et al., 2016; White et al.,
57 2019). How plants recognize and react differently to friends versus foes is an intriguing topic of
58 research.

59 Our understanding of plant immunity has been revolutionized by the recent increase in the
60 breadth of genomic data available. The classical, binary view of plant immunity consists of
61 pattern-triggered immunity (PTI) and effector-triggered immunity (ETI) (Jones and Dangl, 2006;
62 Cui et al., 2015). Plant PTI relies on plasma membrane (PM)-localized pattern recognition
63 receptors (PRRs), which are often receptor-like proteins/kinases (RLPs/RLKs) that sense
64 conserved microbe-associated molecular patterns (MAMPs) or damage-associated molecular
65 patterns (DAMPs) and induce downstream defense reactions (Bigeard et al., 2015; Dodds and
66 Rathjen, 2010; Jones and Dangl, 2006; Zhou et al., 2020). Plant ETI employs an intracellular
67 nucleotide-binding site and leucine-rich repeat domain receptors (NLRs) that recognize specific
68 microbial effectors as a result of ongoing host-pathogen coevolution (Jones and Dangl, 2006; Cui
69 et al., 2015; Wang et al., 2020b; Cesari, 2018; Monteiro and Nishimura, 2018). The oftentimes
70 blurry boundary between MAMPs and effectors prompted a new spatial immunity model based
71 on extracellular or intracellular locations of pattern recognition (Wang et al., 2020b; van der
72 Burgh and Joosten, 2019).

74
75 The comparative study by Baetsen-Young and colleagues (2020) revealed transcriptional
76 reprogramming of *Fusarium virguliforme* when interacting with different plant hosts (soybean
77 versus maize). This study investigated transcriptome reprogramming of the same plant host and
78 explored how PTI and ETI or extracellular and intracellular immunity are involved in both
79 beneficial and antagonistic interactions. We established the *Fusarium oxysporum*–*Arabidopsis*
80 *thaliana* model system, which includes an endophyte, *F. oxysporum* strain Fo47, and a pathogen,
81 *F. oxysporum* strain Fo5176. *Arabidopsis* plants infected by these two *F. oxysporum* strains
82 display distinctive phenotypes, with Fo5176 causing typical vascular wilt diseases and Fo47
83 colonizing plants endophytically without any disease symptoms. Their distinct effects on plants,
84 combined with their minimal genetic diversity (the two strains belong to the same species),
85 should facilitate the identification of meaningful genotype–phenotype correlations.

86
87 In addition to being a good model system, *F. oxysporum* is of great agricultural importance, as it
88 is listed among the top 10 most researched fungal pathogens for food production (Dean et al.,
89 2012). Collectively, this group of filamentous fungi causes devastating vascular wilt diseases in

90 over 100 crop species, leading to annual yield losses of billions of dollars (Ma et al., 2013). One
91 notorious example is the recent Panama disease outbreak in banana caused by *F. oxysporum* f. sp.
92 *cubense* Tropical Race 4 (Viljoen et al., 2020). Information accumulated over the past 10 years
93 has provided a clear picture of compartmentalization of the *F. oxysporum* genome: A core
94 genome component that is conserved and vertically transmitted performs essential housekeeping
95 functions, and an accessory genome that is believed to have been initially acquired horizontally
96 mediates unique host–fungal interactions (Yang et al., 2020; Ma et al., 2010, 2013; Zhang;
97 Vlaardingerbroek et al., 2016b, 2016a; DeJulio et al., 2018; Hane et al., 2011; Williams et al.,
98 2016; Galazka and Freitag, 2014; Armitage et al., 2018; van Dam et al., 2016; Dong et al., 2015).
99

100 Using an unbiased approach and taking advantage of two recently released high-quality genome
101 assemblies of Fo47 and Fo5176 (Wang et al. 2020; Fokkens et al. 2020), we employed
102 metatranscriptomics to dissect how *Arabidopsis* plants react to two *F. oxysporum* isolates with
103 distinct lifestyles during the early course of infection. We demonstrated that endophytic infection
104 suppresses host immunity but activates plant nutrient assimilation. By contrast, pathogenic
105 infection activated defense response but suppressed plant developmental functions. Genome
106 comparison of the two isolates revealed unique accessory chromosomes that harbor genes
107 enriched for fungal virulence and detoxification in Fo5176, and cell signaling and nutrient
108 sensing in Fo47. Our study showed that while for both plants and *F. oxysporum*, most genes
109 displayed a similar expression pattern during infections, a small number of genes displayed
110 transcription plasticity between endophytic and pathogenic infections, perhaps leading to the
111 different interaction outcomes.

112

113

114 **RESULTS**

115 **A pathosystem that reveals both endophytic and pathogenic interactions**

116 To dissect beneficial versus pathogenic fungal–plant interactions, we inoculated *Arabidopsis*
117 plants with two *F. oxysporum* strains, the beneficial (endophytic) strain Fo47 and the pathogenic
118 strain Fo5176. The pathogenic fungus Fo5176, initially isolated in Australia (Thatcher et al.,
119 2012; Chen et al., 2015), causes vascular wilt in several Brassicaceae plants, including *A.*
120 *thaliana* (Thatcher et al., 2009; Ma et al., 2010). The endophytic strain Fo47 was originally
121 isolated from disease-suppressing soils (Alabouvette, 1999) and has been used as a biocontrol
122 agent to prevent disease from soil-borne pathogens by inducing the production of plant
123 secondary metabolites and priming host resistance (Aimé et al., 2013; Olivain et al., 2006;
124 Benhamou et al., 2002; Benhamou and Garand, 2001; Veloso and Díaz, 2012).

125

126 We adopted a robust and reproducible root-dipping protocol to inoculate 14-d-old Col-0 plants
127 with a suspension of fungal spores (Thatcher et al., 2012). Plants inoculated with Fo5176
128 developed typical yellowing and wilting symptoms, visible at 6 d post inoculation (DPI) (Figure
129 1A). By then, the fungal hyphae had advanced into the stele of infected roots (Figure 1B), as
130 revealed by staining with 5-bromo-4-chloro-3-indoxyl- α -L-arabinofuranoside (X-ARA), which
131 is hydrolyzed to a blue precipitate by a fungal-derived enzyme (Diener, 2012). Almost all
132 Fo5176-infected plants died within 3 weeks of inoculation (Figure 1C). By contrast, plants
133 inoculated with Fo47 not only stayed healthy (Figure 1A, C), but also showed increased
134 aboveground biomass (Wilcoxon rank-sum test, $p < 0.001$), when compared to mock-inoculated
135 plants (Figure 1D), suggesting that Fo47 may have a growth-promoting effect. X-ARA staining
136 of plant roots inoculated with Fo47 determined that fungal hyphae were restricted to the root
137 outer layers (Figure 1B).

138

139 By comparing to a sister species *F. verticillioides*, accessory chromosomes were identified in
140 both the Fo47 (Wang et al., 2020a) and Fo5176 (Fokkens et al., 2020) genomes, in addition to
141 the 11 core chromosomes (Figure 2), vertically inherited from the common ancestor shared
142 between these two sister species 10–11 million years ago (Ma et al., 2013). The Fo47 genome
143 had one accessory chromosome (chromosome 7, with a length of 4.25 Mb), while the Fo5176
144 genome had four (chromosomes 2, 14, 16, and 18) (Figure 2). The combined length of accessory

145 chromosomes/regions in Fo5176 was 21.63 Mb, including large segments (size > 1 Mb) of
146 chromosomes 4, 10, 11, and 13 that shared no syntenic block with the *F. verticilliodes* genome.
147 Fo47 and Fo5176 accessory chromosomes were enriched in repetitive sequences (Supplemental
148 Figure 1), a common property observed from all accessory chromosomes (Yang et al., 2020).
149 Fo47 accessory genes were significantly enriched for cell signaling and nutrient sensing
150 functions, whereas Fo5176 genes were enriched for functions relating to virulence and
151 detoxification (Supplemental Data Sets 1 and 2). As these two genomes share an almost identical
152 core sequence, we hypothesized that distinct accessory chromosomes in each genome may play
153 important roles in the distinct phenotypic outcomes (disease versus growth promotion).

154

155 **Reprogramming of the plant transcriptome in response to a fungal pathogen or endophyte**
156 To examine the transcriptional regulation underlying the distinct endophytic and pathogenic
157 interactions of the two strains (Figure 1), we sequenced the fungal and host plant transcriptomes
158 from Arabidopsis plants inoculated with Fo47 or Fo5176. Infected plants were sampled at 12, 24,
159 48, and 96 h post inoculation (HPI), in parallel with plants mock-inoculated with water at 12 HPI
160 as a control. We harvested root tissues for transcriptome deep sequencing (RNA-seq). Dual
161 RNA-seq data were analyzed using an in-house pipeline to calculate the transcript levels of plant
162 and fungal genes.

163

164 About half of all annotated Arabidopsis genes (16,544 out of a total of 32,833) were
165 differentially regulated in at least one of 18 comparisons between different time points for the
166 same interaction type (12, 24, 48, and 96 HPI; 12 comparisons), between different interaction
167 types at the same time point (beneficial versus pathogenic; four comparisons), or between
168 endophytic or pathogenic interactions and the mock control at 12 HPI (two comparisons). These
169 differentially expressed genes (DEGs) revealed several interesting patterns (Figure 3A).

170

171 First, we observed a strong correlation between patterns of gene expression for both treatments at
172 the same time points, despite clearly distinctive endophytic and pathogenic phenotypes (Figure
173 1). The Pearson's correlation coefficients (PCCs) for the four comparisons between plants
174 infected with either the beneficial or the pathogenic fungal strain at each time point were very
175 high, with values of 0.95, 0.94, 0.97, and 0.96 at 12, 24, 48, and 96 HPI, respectively (labeled in

176 red in Figure 3A), suggesting that a small subset of genes contribute to the observed phenotypic
177 differences. Global clustering analysis using the 16,544 Arabidopsis DEGs yielded 24 co-
178 expression gene clusters (Figure 3B, Supplemental Figure 2, Supplemental Data Set 3). A total
179 of 10,014 genes within 12 clusters had similar expression patterns at all time points (see
180 Supplemental Data Set 3), accounting for 60.5% of all DEGs. Considering the fact that 16,289
181 genes were either not expressed or not changed, we concluded that 6,544 (~20% of all) genes
182 held answers to the transcriptional reprogramming between these two treatments.

183

184 We also observed significant transcriptional reprogramming within each interaction over time.
185 For samples inoculated with Fo47, PCC scores decreased from 0.94 (between 12 and 24 HPI) to
186 0.84 (between 12 and 96 HPI) as infection progressed. Similarly, PCC values dropped from 0.93
187 (between 12 and 24 HPI) to 0.81 (between 12 and 96 HPI) for Fo5176-inoculated plants. We
188 then compared each fungal interaction pairwise at each time point to identify reciprocal DEGs
189 (Supplemental Figure 3A), yielding 1,009, 642, 59, and 403 genes that were preferentially
190 expressed in Fo47-infected plants and 868, 1,172, 604, and 425 plant genes in Fo5176-infected
191 plants at 12, 24, 48, and 96 HPI, respectively (Supplemental Figure 3B). Notably, plant genes
192 that were preferentially expressed during the endophytic interaction were enriched in Gene
193 Ontology (GO) terms such as cell cycle, cell growth, development, response to stimuli, and
194 cellular transport. Moreover, the genes associated with each enriched GO term showed a
195 temporal wave as the infection course progressed, with genes involved in cell cycle highly
196 enriched at the early stages of infection, but with a diminishing contribution that was
197 consecutively replaced by genes related to development at around 24 HPI, response to stimuli at
198 48 HPI, and transport at 96 HPI (Supplemental Figure 3C). Conversely, genes preferentially
199 induced in response to the pathogenic fungus were consistently enriched in GO terms mainly
200 related to defense responses, with no obvious underlying temporal pattern (Supplemental Figure
201 3C).

202

203 Second, when compared to the mock-inoculated samples, plants inoculated with Fo47 or Fo5176
204 both displayed drastic transcriptional reprogramming at the earliest time point of this study (12
205 HPI), as these comparisons had the lowest PCCs of 0.85 for Fo47 and 0.83 for Fo5176. As time
206 from initial inoculation progressed, however, the transcriptomes of all plants became much more

207 similar, with PCCs rising to 0.98 for Fo47 and 0.96 for Fo5176 (labeled in green in Figure 3A).
208 This observation indicated that the outcome of the plant–host interaction might be decided as
209 early as 12 HPI. To begin to dissect the critical transcriptional reprogramming taking place at 12
210 HPI in both endophytic and pathogenic interactions, we conducted a careful analysis to identify
211 genes that are not only differentially expressed between the two treatments, but also
212 differentially expressed relative to mock-inoculated samples. This analysis resulted in the
213 identification of genes that were specifically upregulated or downregulated in fungus-infected
214 samples. These four plant gene sets consisted of 140 upregulated and 422 downregulated genes
215 specifically in response to Fo47 infection, and 286 upregulated and 767 downregulated genes in
216 response to Fo5176 infection.

217

218 Functional analysis of these genes using GO enrichment and network analyses (Figure 4,
219 Supplemental Data Set 4–7) confirmed previous observations of fungal–plant interactions but
220 also revealed unexpected findings. As expected, we observed significant suppression of genes
221 related to plant growth by the pathogenic strain Fo5176 (Figure 4A), including genes associated
222 with the cell cycle, cell wall organization, plant-type cell wall biosynthesis, and microtubule-
223 based processes. Genes upregulated early in response to Fo5176 infection were highly enriched
224 in toxin and indole metabolism, as well as small molecule biosynthesis (Figure 4B), possibly
225 reflecting the initial upheaval brought upon by the infection. For the endophytic interaction, we
226 noticed a significant suppression of immunity-related functions, including plant
227 defense/immunity and jasmonic acid response (Figure 4C). This data therefore also suggested
228 that the endophytic strain Fo47 attenuates plant defenses. Among the genes induced by the
229 endophyte, we were pleased to see that several define a module related to nitrate metabolism and
230 anion transport (Figure 4D), which would be consistent with the promotion of plant growth by
231 Fo47 (Figure 1D).

232

233 A nitrate–CPK (Ca^{2+} -sensor protein kinase)–NLP (Nin-like protein) signaling pathway was
234 previously reported (Liu et al., 2017) that activated the expression of 394 genes and repressed
235 another 79 genes in response to exogenous nitrate treatment. We examined whether our clusters
236 of DEGs (Figure 3B) showed an overrepresentation of genes differentially regulated by this
237 nitrate signaling pathway. Cluster 21 included the most downregulated genes from this pathway,

238 with eight genes (p -value = 2.56e-04, two-sided Fisher's exact test) that were downregulated in
239 both interactions, with stronger suppression by the endophyte (Supplemental Figure 2,
240 Supplemental Data Set 8). Of the 394 upregulated genes in the nitrate pathway, 329 were
241 differentially expressed in our data set, with 251 assigned to clusters. Of those, over half were
242 significantly enriched in five clusters: C5 (20 genes, p -value = 2.12e-05), C6 (14 genes, p -value
243 = 1.07e-05), C8 (40 genes, p -value = 1.46e-14), C16 (16 genes, p -value = 7.37e-04), and C23
244 (38 genes, p -value = 6.62e-21). These 251 genes, representing a majority of the genes
245 upregulated in the nitrate signaling pathway, were induced by both the endophyte and the
246 pathogen but exhibited stronger responses in the context of endophytic inoculations
247 (Supplemental Figure 2).

248

249 Notably, cluster C23 included *NLP1*, encoding a transcription factor involved in the nitrate–
250 CPK–NLP signaling pathway (Liu et al., 2017), as well as *NITRATE TRANSPORTER2.1* and 2.2
251 (*NRT2.1*, *NRT2.2*), *NITRATE REDUCTASE1* (*NIA1*), and *NITRITE REDUCTASE1* (*NIR1*), all
252 major components of the pathway that were upregulated when compared to the mock-inoculated
253 sample (Supplemental Figure 4). Out of 24 previously reported transcription factors that control
254 transcriptional regulation of nitrogen-associated metabolism and growth (Gaudinier et al., 2018),
255 16 of them were assigned to our clusters (Supplemental Data Set 9), including *WUSCHEL*
256 *RELATED HOMEOBOX14* (*WOX14*) and *LOB DOMAIN-CONTAINING PROTEIN4* (*LBD4*) in
257 cluster C23. Collectively, this analysis suggests that nitrogen signaling is involved in the *F.*
258 *oxysporum*–Arabidopsis interaction and the endophyte may enhance the nitrogen signal and
259 hence change the course of the plant response.

260

261 Perturbation of plant immunity

262 To better understand how the endophyte and the pathogen perturb plant immunity via shared and
263 distinct responses, we carefully investigated the 24 co-expression clusters based on their global
264 patterns of expression. Four clusters, C7, C15, C16, and C21, showed enrichment ($p < 0.05$) for
265 GO terms related to immunity and defense responses; the same clusters also lacked GO terms
266 related to development (Figure 3C). Compared to plant PTI and ETI networks (consisting of
267 1,856 PTI-related and 1,843 ETI-related genes) previously constructed using a machine learning
268 algorithm (Dong et al., 2015), three clusters (C15, C16, and C21) were enriched for both PTI and

269 ETI genes, whereas cluster C7 was primarily enriched in PTI response genes (two-sided Fisher's
270 exact test $p < 0.05$) (Supplemental Data Sets 10 and 11). This suggests a transcriptional plasticity
271 of plant immunity in responding to the endophytic and pathogenic *F. oxysporum*.

272

273 ***Conserved immune response toward an endophyte and a pathogen***

274 Cluster C15 comprised 1,290 genes and was the largest immunity-related cluster, with nearly
275 identical plant transcriptome responses following Fo47 and Fo5176 inoculation. Indeed, genes
276 from cluster C15 were initially strongly upregulated at 12 HPI in both interactions and gradually
277 returned to an expression level comparable to that of mock-inoculated plants as infection
278 progressed (Figure 5A). C15 was most significantly enriched in PTI genes (p -value = 2.66e-72),
279 reflecting the general plant perception of fungal signals derived from both pathogenic and
280 symbiotic organisms (e.g. MAMPs). Cluster C15 indeed included many immunity-related genes
281 involved in fungal perception, signal transduction, and transcriptional regulation, including
282 *ERECTA*, a RLK that regulates stomatal patterning and immunity (Sopeña-Torres et al., 2018);
283 *RECOGNITION OF PERONOSPORA PARASITICA5 (RPP5)*, which encodes a putative NLR
284 protein that confers resistance to *Peronospora parasitica* (Noël et al., 1999; Parker et al., 1997);
285 *RESPONSIVE TO DEHYDRATION 21A (RD21A)*, which encodes a cysteine proteinase with
286 peptide ligase and protease activity that is involved in immune responses against the
287 necrotrophic fungal pathogen *Botrytis cinerea* (Lampl et al., 2013); and *NUCLEAR FACTOR Y,*
288 *SUBUNIT B3 (NF-YB3)*, which encodes a transcription factor activated by endoplasmic
289 reticulum (ER) stress responsible for the regulation of stress responses (Liu and Howell, 2010).

290

291 Cluster C15 was also highly enriched in genes with functions related to the chloroplast/plastid
292 (p -value = 9.2e-89, Figure 5B, Supplemental Data Set 12). An organelle essential for plant
293 photosynthesis, chloroplasts have recently come to the forefront as key players in plant immune
294 responses (Göhre et al., 2012; Serrano et al., 2016), possibly functioning as a signaling hub that
295 links the initial recognition of diverse pathogens at the PM and signal transduction to the nucleus
296 to orchestrate transcriptional reprogramming in response to infection (Medina-Puche et al., 2020;
297 Chan et al.; de Souza et al., 2017; Wang et al., 2016; de Torres Zabala et al., 2015; Liu, 2016). It
298 is unlikely that chloroplast-related genes from cluster C15 represent artifacts caused by the
299 manipulation of roots in the light during harvesting, as these genes were expressed at low levels

300 in mock-inoculated plants, although they were subjected to the same inoculation and harvesting
301 procedure. Our observations are also consistent with a previous report in which strain Fo5176
302 was shown to induce the expression of *Arabidopsis* genes normally involved in photosynthesis in
303 root tissues at 1 DPI (Lyons et al., 2015). Pathogens may thus interfere with host
304 chloroplast/plastid functions to manipulate host immunity in their favor. We know very little
305 about the possible role played by chloroplasts during endophytic colonization.
306

307 ***Stronger induction of plant PTI responses by the pathogen***

308 We hypothesized that a subset of plant immune responses against the pathogen and endophyte
309 would differ, given their distinctive phenotypes, even though most clusters showed the same
310 pattern during endophytic and pathogenic responses. Indeed, three immunity-related clusters, C7,
311 C16, and C21, exhibited distinct patterns between the pathogen and the endophyte (Figure 5A).
312 Cluster C7 (422 genes), which was primarily enriched in genes associated with PTI, exhibited a
313 stronger induction by Fo5176 infection than by Fo47, despite being induced by both strains
314 (Figure 5A). Several GO terms were shared between clusters C7 and C15, such as
315 chloroplast/plastid-related functions (Figure 5B), possibly reflecting fine-tuning of the initial
316 recognition of conserved fungal signals.
317

318 Interesting genes included *PEROXIDASE37 (PRX37)*, encoding a putative apoplastic peroxidase
319 that generates H₂O₂ primarily in the vascular bundles for host defense (Pedreira et al., 2011), and
320 *PENETRATION2 (PEN2)*, encoding an atypical tyrosinase required for broad-spectrum
321 resistance to filamentous plant pathogens (Fuchs et al., 2016). Also included in cluster 7 were
322 genes with dual functional roles in immunity against different pathogens. For instance,
323 *PATATIN-LIKE PROTEIN2 (PLP2)* promotes cell death and facilitates *Botrytis cinerea* and
324 *Pseudomonas syringae* infection in *Arabidopsis* (La Camera et al., 2005), whereas it confers host
325 resistance to Cucumber mosaic virus (Camera et al., 2009). *KUNITZ TRYPSIN INHIBITOR1*
326 (*KTII*), a trypsin inhibitor referred as an antagonist involved in the negative regulation of
327 programmed cell death that mediates susceptibility in *Erwinia carotovora* but has an opposite
328 function in *Pseudomonas syringae* pv *tomato* DC3000 (Li et al., 2008).
329

330 ***Suppressed plant immunity in the presence of the endophyte***

331 In contrast to clusters C7 and C15, both clusters C16 (615 genes) and C21 (766 genes) exhibited
332 stronger suppression of expression by the endophyte (Figure 5A). We also observed a unique and
333 specific suppression of plant immunity by the endophyte from the GO term enrichment and
334 network analyses at 12 HPI described above (Figure 4C). While clusters C7 and C15 showed
335 minimal overlap of enriched GO terms, clusters C16 and C21 shared many terms, including
336 signal perception and transduction, protein–protein interaction, and PM localization (Figure 5B).
337 Out of 70 genes identified as contributing to danger sensing and signaling systems (Zhou and
338 Zhang, 2020), we detected 12 genes in cluster C16 and another 12 genes in cluster C21 (Table 1
339 and Supplemental Data Set 13). For instance, PRRs and downstream components in cluster C16
340 include *EFR*, *BAK1*, *LYK5*, and *CERK1*; and *PEPR1*, *PEPR2*, *FERONIA*, and *RBOHD* in cluster
341 C21. NLRs and downstream signaling components in cluster C16 include *ADR1-L1/ADR1-L2*
342 and *RPM1*, *PAD4*, and *RPS4* in cluster C21. In summary, a strong suppression of diverse
343 immunity-related genes is unique to the endophytic interaction, suggesting that modulation of
344 plant immunity may contribute to the different outcomes.
345

346 **A systematic analysis of PTI- and ETI-sensing genes induced by the endophyte and the**
347 **pathogen**

348 Overall, we observed strong host immune responses when challenged with either the endophyte
349 or the pathogen, involving complex signal perception and signal transduction cascades. Distinct
350 responses included the suppression of plant growth and the induction of plant defenses by the
351 pathogenic strain Fo5176 and the attenuation of host immunity with the concomitant induction of
352 nitrogen metabolism by the endophytic strain Fo47 (Figure 4). To further dissect the plant
353 immunity pathways involved in these two interactions, we conducted a systematic analysis of the
354 expression profiles of genes encoding RLPs/RLKs and NLR proteins (See supplementary data 14
355 and 15 and examples in Table 1).
356

357 ***RLP/RLK* genes**

358 The Arabidopsis genome encodes 533 RLPs/RLKs, as determined by the MAPMAN Mercator
359 annotation (Schwacke et al., 2019). Of those, 311 were assigned to our clusters of DEGs
360 (Supplemental Data Set 14). In addition to the two immunity clusters C16 (37 genes, *p*-value =
361 4.76e-11) and C21 (30 genes, *p*-value = 2.11e-05), whose expression is repressed by the

362 endophyte, these *RLP/RLK* genes were also enriched in clusters C11 (14 genes, *p*-value = 6.31e-
363 04) and C12 (11 genes, *p*-value = 6.31e-04). Their expression appeared to be repressed by both
364 the endophyte and the pathogen to varying degrees. Characterized defense-related *RLK* genes
365 include *SUPPRESSOR OF BIR1 (SOBIR1)* and *EFR* in cluster C16 and *RESISTANCE TO*
366 *FUSARIUM OXYSPORUM1 (RFO1)* and *PROLINE-RICH EXTENSIN-LIKE RECEPTOR*
367 *KINASE1 (PERK1)* in cluster C21. *RFO1* encodes a protein that confers a broad-spectrum
368 resistance to *Fusarium* (Diener and Ausubel, 2005). Cluster C16 also included genes encoding
369 LysM receptor-like kinases *CERK1* and *LYK5* (Cao et al., 2014), which are essential for the
370 perception and transduction of the chitin oligosaccharide elicitor. Although not significantly
371 enriched, 26 *RLP/RLK* genes grouped in cluster C15, including *FLG22-INDUCED RECEPTOR-*
372 *LIKE KINASE1 (FRK1)* and *HERCULES RECEPTOR KINASE1 (HERK1)*, which are activated
373 in response to both pathogenic and endophytic *F. oxysporum* strains.
374

375 ***NLR* genes**

376 Many plant NLRs are commonly identified as resistance proteins that act as surveillance
377 molecules recognizing pathogen effectors that target the host machinery. In accordance with the
378 so-called “guard” model, NLRs then trigger an ETI response (Cao et al., 2014). The *Arabidopsis*
379 genome encodes 160 NLR proteins (Baggs et al., 2020), of which we identified 119 genes among
380 our data set of DEGs (84 were assigned to clusters). Among these NLR genes, about 40%
381 clustered across four immunity clusters, cluster C21 (18 genes), C16 (14 genes), C15 (11 genes),
382 and C7 (4 genes), and were uniquely enriched in clusters 21 (*p*-value = 2.58e-07) and 16 (*p*-
383 value = 6.82e-06), both of which include genes specifically repressed in the endophyte
384 (Supplemental Data Set 15). The 11 NLR genes in cluster C15 included five known resistance
385 genes (AT1G63880, AT1G61190, RPP4, RPP5, and RPP8) against oomycete and fungal
386 pathogens (Goritschnig et al., 2012; McDowell et al., 2005; Staal et al., 2006; van der Biezen et
387 al., 2002).

388 Notably, most of the *NLR* genes that were enriched in endophyte-suppressed clusters C16 and
389 C21 are not functionally characterized. Nevertheless, characterized NLRs represented by genes
390 in cluster C16 included two apoplast/chloroplast-localized ADP-binding immune receptors
391 (ADR1-L1 and ADR1-L2) (Dong et al., 2016). Also belonging to cluster C16 were the two

393 effector-induced resistance genes *LAZARUS5* (*LAZ5*) and *HOPZ-ACTIVATED RESISTANCE1*
394 (*ZARI*) (Barbacci et al., 2020; Baudin et al., 2017), conferring resistance to a *Pseudomonas*
395 *syringae* strain expressing the AvrRPS4 and Hop effectors, respectively. *NLR* genes in cluster
396 C21 included disease resistance proteins RPS3, RPS4, and RPS6, which provide specific
397 resistance against *P. syringae* pv. *tomato* carrying the avirulence genes *AvrRPS3*, *AvrRPS4*, and
398 *AvrRPS6*, respectively (Narusaka et al., 2009; Kim et al., 2009; Bisgrove et al., 1994).
399 Repression of the expression of these *NLR* genes by the endophyte again supports the idea that
400 the danger sensing and signaling systems underlying the responses to Fo47 and Fo5176 are
401 distinct.
402

403 **Accessory chromosomes in two strains harbor genes induced during infection and with 404 distinct biological functions**

405 The distinct plant responses at both the phenotypic and transcriptome levels, resulting from
406 inoculation with the two *F. oxysporum* isolates, is in no doubt related to genomic differences
407 between the two strains. Even though both strains belong to the same species complex and share
408 an ~46-Mb core genome, each strain also carries distinct accessory chromosomes (Figure 2). The
409 Fo47 accessory chromosome 7 harbored 1,299 predicted genes (7.2% of total predicted genes)
410 (Supplemental Data Set 16), 757 of which were expressed and 160 were strongly induced (false
411 discovery rate (FDR) < 0.05) during one or more time points of the infection.
412

413 To explore the function of these accessory genes encoded in the endophytic strain Fo47, we next
414 analyzed the functional domains they encoded. After excluding genes that encoded proteins with
415 transposase-like domains or unknown domains, we highlighted five enriched PFAM domains:
416 regulator of G-protein signaling domain (PF00615), nitric oxide (NO)-binding membrane sensor
417 involved in signal transduction (PF03707), basic Leucine Zipper (bZIP) transcription factor
418 (PF00170), chromodomain (PF00385), and bromodomain (PF00439) (Figure 6A, Supplementary
419 Figure 5A). The enrichment of functional domains involved in cell signaling and the apparent
420 lack of enrichment for domains related to virulence suggested that the Fo47 accessory
421 chromosome contains genes with functions that are well suited to a nonpathogenic life style.
422 Transcriptome analysis showed that nine Fo47 genes encoding proteins with the bacterial
423 signaling protein domain (PF03707) are most highly induced at 24 and 48 HPI. Domain

424 PF03707 plays a role in sensing oxygen, carbon monoxide (CO), and NO (Galperin et al., 2001).
425 The Fo47 genome has the highest number of genes encoding a PF03707 domain, with nine genes,
426 compared to other filamentous fungi such as *Aspergillus nidulans* (1), *Neurospora crassa* (1),
427 *Magnaporthe grisea* (1), *F. graminearum* (2), *F. verticillioides* (2), and *F. solani* (3) (Galagan et
428 al., 2005; Cuomo et al., 2007; Dean et al., 2005, Ma et al., 2010), as well as other FOSC
429 members (3 ~ 7, average 4) (DeJulio et al., 2018). Notably, six of the nine genes reside on
430 accessory chromosome 7, making it a major contributor to the expansion of this gene family
431 within this strain (Supplemental Figure 6).

432

433 By contrast, accessory chromosomes and regions from the pathogenic strain Fo5176 contributed
434 4,136 predicted genes (23% of total predicted genes) (Supplemental Data Set 17), of which 3,502
435 were expressed and 1,140 were strongly induced during one or more time points of the infection.
436 Genes located in accessory regions in Fo5176 encoded proteins that were enriched for 42 PFAM
437 domain terms. We noticed six PFAM domains that were highly enriched at different stages of the
438 infection course and whose encoding genes were highly expressed: cysteine-rich secretory
439 protein family (PF00188), Calpain family cysteine protease (PF00648), peptidase M16
440 (PF16187), poly (ADP-ribose) polymerase regulatory domain (PF02877), cyclin C-terminal
441 domain (PF02984), and WGR domain (PF05406) (Figure 6B, Supplementary Figure 5B). Most
442 of these domains are likely associated with microbial pathogenesis or detoxification; their
443 associated genes were induced during infection (Figure 6B). In particular, members of the
444 cysteine-rich secretory protein (CAP) superfamily (PF00188) have a wide range of biological
445 activities, including fungal virulence, cellular defense, and immune evasion (Schneiter and Di
446 Pietro, 2013). For example, the *F. oxysporum* CAP family protein Fpr1 is a PR-1-like protein
447 that is important for the virulence of strain Fol4287 (Prados-Rosales et al., 2012). The Fo5176
448 genome encodes 15 CAP family members, significantly more than Fo47 and other comparable
449 fungal species (average: 5 members) (Supplemental Figure 7). Phylogenetic analysis of CAP
450 proteins showed that four CAP members formed a core group shared by Fo5176 and Fo47.
451 However, a separate clade of six CAP family proteins was expanded in Fo5176 and encoded by
452 Fo5176 accessory chromosomes (Supplemental Figure 7). These results highlight the distinctive
453 functions of, and roles played by, accessory chromosomes in the nonpathogenic strain Fo47 and
454 the pathogenic strain Fo5176. These differences might provide the mechanistic basis that allows

455 Fo47 to specialize in host sensing and benefit its host as an endophyte, while the pathogenic
456 Fo5176 specializes in host invasion and killing.

457

458

459 **DISCUSSION**

460 We performed a comparative study of infection by an endophytic (Fo47) and a pathogenic
461 (Fo5176) strain of *F. oxysporum* in the context of the *F. oxysporum* Arabidopsis system, which
462 revealed the transcriptional plasticity of plant defense responses. The pathosystem we developed
463 combines the extensive knowledge of plant immunity in Arabidopsis and one of the most
464 damaging fungal pathogens for agriculture, *F. oxysporum*. Strain-specific interactions with a
465 common host are likely dictated by the accessory chromosomes from each *F. oxysporum* genome,
466 which allows a comparative study that minimizes genetic differences between strains to address
467 the underlying mechanism that results in distinct phenotypes (growth promotion or disease or
468 even death). Up to 50% of crop losses in the USA can be attributed to soil-borne pathogens
469 (Raaijmakers et al., 2009), and our results provide a foundation for the development of
470 technologies to enhance plant health, sustain a healthy ecosystem, and feed a continuously
471 growing human population.

472

473 We employed comparative metatranscriptomics over the course of early infection to
474 systematically capture temporal transcriptional changes in both the host and the interacting
475 microbes. Our results may be summarized along four main axes, as illustrated in Figure 7.

476

477 First, host transcriptional responses were strikingly similar at all time points, regardless of the
478 obvious phenotypic differences seen after infection of Arabidopsis plants by Fo47 and Fo5176.
479 Of all clusters of DEGs, cluster C15 exhibited a strong and early induction of genes, followed by
480 a return to an expression level comparable to that of control samples. This cluster captured 26
481 Arabidopsis *RLP/RLK* genes, as well as 269 PTI and 159 ETI response genes, suggesting that
482 both strains initially elicit a similar MAMP response, which would not be surprising as they
483 belong to the same species.

484

485 Second, our data revealed rapid transcriptional reprogramming at the beginning of the
486 interactions. While the majority of plant genes exhibited a common expression pattern during the
487 two infections, a small subset of plant genes displayed divergent gene expression profiles. By far
488 the most striking difference was observed at 12 HPI, when the GO biological processes for genes
489 uniquely induced by Fo47 or Fo5176 reflected almost opposite responses. The endophytic strain

490 Fo47 stimulated nitrogen metabolism and suppressed host immunity, whereas the pathogenic
491 strain Fo5176 stimulated host immune responses and toxin metabolism, but repressed functions
492 related to plant growth and development. We propose that this distinct expression profile,
493 reflected in the early divergence of the host transcriptome, is the result of plasticity of the host
494 transcriptome when facing an endophyte or a pathogen. We hypothesize that the perception by
495 the host of distinct fungal signals occurs shortly after inoculation and is followed by the rapid
496 activation of downstream signaling cascades. Our results also stress the importance and necessity
497 of sampling early during the establishment of a fungal–host interaction to better capture the full
498 extent of the underlying temporal dynamics.

499

500 Third, Fo47 inoculation resulted in suppression of genes related to plant defense and induced
501 genes related to plant growth, in agreement with the trade-off between growth and defense. It has
502 been reported that plants can channel nitrogen resources towards production of defense-related
503 compounds when confronted with pathogens (Ullmann-Zeunert et al., 2013). For instance, allele
504 polymorphism at the single locus *ACCELERATED CELL DEATH6* (*ACD6*) can dictate distinct
505 difference between growth and defense among different *Arabidopsis* ecotypes (Todesco et al.,
506 2010). Further characterizing the *F. oxysporum*–*Arabidopsis* pathosystem should illuminate the
507 mechanism(s) by which nutrients are allocated in relation to plant defense.

508

509 Finally, we observed an agreement between plant infection phenotypes and distinctive gene
510 functions associated with fungal accessory chromosomes. While upregulated fungal accessory
511 genes were primarily enriched in proteins with roles in cell signaling and nutrient transport in the
512 endophyte Fo47, they were enriched for virulence and detoxification in the pathogen Fo5176,
513 likely contributing to the contrasting phenotypes of plants infected by these two *F. oxysporum*
514 strains.

515

516 In conclusion, time-resolved comparative metatranscriptomics can be used to characterize
517 transcription regulation when the model plant *Arabidopsis* is challenged with an endophyte and a
518 pathogen of the same fungal species. We showed both the conservation and plasticity of the plant
519 and fungal transcriptomes and how they may relate to the distinctive genomic features associated
520 with each fungal genome. The *Arabidopsis* and *F. oxysporum* pathosystem developed here is

521 likely to become an ideal system to characterize plant recognition and response mechanisms
522 against soil-borne root fungi. We believe this system will be pivotal in enriching our
523 understanding of the molecular mechanisms necessary to enhance vascular wilt resistance not
524 only in *Arabidopsis*, but also in crops that are under threat by *F. oxysporum* pathogens.

525

526

527

528 **METHODS**

529 **Plant and fungal growth**

530 *Fusarium oxysporum* strains Fo5176 and Fo47 were routinely cultured on potato dextrose agar
531 (BD, New Jersey USA) at 28°C under a 12-h-light/12-h-dark photoperiod. Fungal spores were
532 collected from 5-d-old cultures in potato dextrose broth (BD, New Jersey USA) by passing the
533 liquid culture through a double layer of sterile cheesecloth, followed by centrifugation of the
534 flow-through at 3,000 g for 15 min at room temperature. Fungal spores were mixed with an
535 appropriate volume of sterile deionized water to prepare the spore suspension (concentration: 1 ×
536 10⁶ spores/mL) for infection assays.

537

538 **Plant infection assay**

539 Seeds of Arabidopsis (*Arabidopsis thaliana*) accession Columbia-0 (Col-0) were obtained from
540 the Arabidopsis Biological Resource Center (ARBC, Ohio State University) and were surface
541 sterilized in 1 mL of 70% (v/v) ethanol three times, 5 min each, followed by one wash with 50%
542 (v/v) bleach for 5 min. After removing the bleach solution, seeds were rinsed with 1 mL of
543 sterile distilled and deionized water, and stratified for 3–4 d in darkness at 4°C. Seeds were
544 planted into pots filled with an autoclaved mixture of fine-grain play sand: MetroMix
545 360:vermiculite in a 1:2:1 ratio, watered with distilled deionized water, and covered with a clear
546 plastic lid to retain a high humidity for 3 d in the growth chamber with the following settings:
547 24°C, 14 h light/10 h dark, and a light intensity (T8 fluorescent and incandescent bulbs) ranging
548 from 89 to 94 $\mu\text{mol}\cdot\text{m}^{-2}\cdot\text{s}^{-1}$. After 3 d, the plastic lid was removed, and seedlings were allowed
549 to grow for 11 additional days prior to inoculation with *F. oxysporum* microconidia. Plants were
550 14 d old at the time of inoculation and had at least four fully expanded true leaves. For *F.*
551 *oxysporum* infection, the roots of 14-d-old Arabidopsis plants were dipped for 30 s in a 1 × 10⁶
552 fungal spores/mL suspension of Fo5176 or Fo47, or in sterile dH₂O for the mock control.
553 Inoculated plants were planted in autoclaved potting mix and moved to a growth chamber set to
554 28°C with the same photoperiod as above.

555

556 **RNA preparation, sequencing, and data analysis**

557 Roots from infected plants at 12, 24, 48, and 96 h post inoculation (HPI) were harvested from
558 five plants per treatment and time point for total RNA isolation. For control samples, roots from

559 the same number of control plants were collected at 12 HPI. Fungal cultures from Fo5176 and
560 Fo47 fungal mycelia were harvested after 5 d from liquid cultures for RNA extraction. Three
561 biological replicates were produced for each treatment. Total RNA was extracted using the ZR
562 Soil/Fecal RNA Microprep Kit (Zymo Research, CA, Cat. R2040) following the manufacturer's
563 protocol, and the RNA quantity and quality were assessed using a NanoDrop 2000 and Agilent
564 2100 Bioanalyzer. Illumina TruSeq stranded mRNA libraries were prepared and sequenced on an
565 Illumina HiSeq2000 platform at the Broad Institute (Cambridge, MA). One replicate each for
566 infected plant samples inoculated with Fo47 at 12 HPI and Fo5176 at 24 HPI failed, as did one
567 replicate for Fo47 and Fo5176 mycelia samples; these four conditions are therefore only
568 represented by two replicates and were used for downstream processing and analysis.
569

570 Paired-end RNA-seq reads were first assessed for quality by FastQC 0.10.1 (Andrews, 2010).
571 RNA-seq data were analyzed using the HISAT, StringTie, and DESeq2 pipelines (Pertea et al.,
572 2016; Love et al., 2014). Briefly, reads were mapped to reference genomes of Arabidopsis
573 (annotation version Araport11, (Cheng et al., 2017)), Fo5176 (Like Fokkens et al., 2020), and
574 Fo47 (Wang et al., 2020a) using HISAT2/2.0.5 (Kim et al., 2015). Mapped reads were used to
575 quantify the transcriptome by stringTie/1.3.4 (Pertea et al., 2015). Read count normalization and
576 differential gene expression analysis were conducted using DESeq2/1.27.32 with a maximum
577 FDR of 0.05 (Love et al., 2014). Corrplot/0.84 was used to visualize the correlation in gene
578 expression profiles between different conditions. Read counts of differentially expressed genes
579 (DEGs) were first averaged per condition and then normalized by log transformation as
580 $\log_2(\text{normalized read count} + 1)$, and then correlations were calculated. Clustering analysis on
581 per-condition averaged, log-transformed, and Z-scaled read counts was performed using the K-
582 means clustering algorithm 'Lloyd' (R function K-means) and then visualized in ggplot2/3.3.0.
583

584 **Functional analysis and visualization**

585 GO enrichment analysis (plant GO slim) of Arabidopsis gene clusters and reciprocal DEG
586 analysis were conducted with the singular enrichment analysis (SEA) tool of agriGO v2 (Du et
587 al., 2010; Tian et al., 2017) using the Arabidopsis TAIR10 annotation. We applied a
588 hypergeometric test, combined with Hochberg (FDR) multi-test adjustment method to discover
589 enriched GO terms at a significance level of 0.01 with a minimum of three mapping entries.

590 Comparisons of different enrichment results were performed using cross-comparison of SEA
591 (SEACOMPARE). We generated PFAM annotations for *F. oxysporum* 5176 and 47 by
592 InterproScan, following a standard annotation pipeline (Jones et al., 2014). PFAM enrichment in
593 proteins encoded by fungal genes was performed in TBtools (Chen et al., 2020) using Fisher's
594 exact test with FDR < 0.05. We performed a custom analysis in Metascape (Zhou et al., 2019),
595 with the options minimum overlap of 3, *p*-value cutoff of 0.01, and minimum enrichment of 1.5
596 for the discovery of GO term enrichment and network visualization of Arabidopsis DEGs at 12
597 HPI. The top five terms (with the smallest *p*-values) were selected, and the terms that shared the
598 gene entries (forming edges) were visualized. The visualization was further polished in
599 Cytoscape/3.8.0 (Shannon, 2003).

600

601 **Synteny and phylogenomic analysis**

602 Synteny was detected by Basic Local Alignment Search Tool for nucleotides (BLASTN), with
603 parameters above 50 kb coverage and 98.5% sequence identity, and visualized as a Circos plot
604 (Krzywinski et al., 2009). *OrthoFinder* was used to identify orthologous pairs across compared
605 genomes and to construct a genome-based phylogenetic tree. The divergence times between
606 species were estimated using the PL method with r8s (Taylor and Berbee, 2006). CAFE
607 (Computational Analysis of gene Family Evolution) v.3 (Han et al., 2013) was used to test
608 whether protein family sizes were compatible with a stochastic birth and death model, and the
609 Viterbi algorithm in the CAFE program was used to assign *p*-values to the
610 expansions/contractions experienced at each branch and using a cutoff of *p* < 0.05.

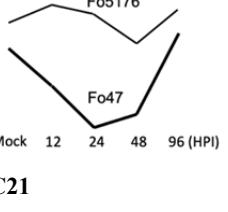
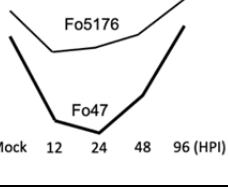
611

612 **Accession Numbers**

613 RNA-seq data generated in this study were deposited in the NCBI Short Read Archive (SRA)
614 with accession number GSE87352.

615

616 **Table 1. Genes that play important roles in danger sensing and signaling suppressed by the endophytic
617 interaction**

Cluster	PRRs and downstream components	RLCKs	MAP kinase cascades	NLRs and downstream signaling	SA biosynthesis and signaling
C16	 <i>EFR</i> <i>BAK1</i> <i>LYK5</i> <i>CERK1</i> <i>SOBIR1</i>	<i>PBL1</i> <i>PBL2</i>	<i>MEKK1</i> <i>MPK11</i>	<i>ADRI-L1</i> <i>ADRI-L2</i> <i>LAZ5</i> <i>ZARI</i>	<i>CBP60g</i> <i>SARD1</i>
C21	 <i>PEPR1</i> <i>PEPR2</i> <i>FER</i> <i>RBOHD</i> <i>PERK1</i> <i>RFO1</i>		<i>MPK3</i>	<i>RPM1</i> <i>PAD4</i> <i>RPPI</i> <i>RPS4</i> <i>RPS3</i> <i>RPS6</i>	<i>CAMTA3</i> <i>NPR1</i> <i>NPR3</i>

619 **Notes:**

- 620 1. Abbreviation of header: receptor-like cytoplasmic kinase [RCLK], mitogen-activated protein
621 [MAP], salicylic acid [SA],
622 2. Abbreviation of genes: *EF-TU RECEPTOR* [*EFR*], *BRI1-ASSOCIATED RECEPTOR
623 KINASE1* [*BAK1*], *LYSM-CONTAINING RECEPTOR-LIKE KINASE5* [*LYK5*], *CHITIN
624 ELICITOR RECEPTOR KINASE1* [*CERK1*], *PEP1 RECEPTOR* [*PEPR*], *FERONIA* [*FER*],
625 *RESPIRATORY BURST OXIDASE HOMOLOGUE D* [*RBOHD*], *AVRPPHB SUSCEPTIBLE1-
626 LIKE1* [*PBL1*], *PBL2*), *MAPK/ERK KINASE KINASE1* [*MEKK1*], *MAP KINASE11* [*MPK11*],
627 *ACTIVATED DISEASE RESISTANCE1-LIKE* [*ADRI-L*], *RESISTANCE TO P. SYRINGAE PV
628 MACULICOLA1* [*RPM1*], *PHYTOALEXIN DEFICIENT4* [*PAD4*], *RECOGNITION OF
629 PERONOSPORA PARASITICA1* [*RPPI*], *RESISTANT TO P. SYRINGAE4* [*RPS4*],
630 *CALMODULIN-BINDING PROTEIN 60-LIKE G* [*CBP60g*], *SA RESPONSE DEFICIENT1*
631 [*SARD1*], *CALMODULIN-BINDING TRANSCRIPTION ACTIVATOR3* [*CAMTA3*],
632 *NONEXPRESSER OF PATHOGENESIS-RELATED GENE* [*NPR*], *SUPPRESSOR OF BIR1*
633 [*SOBIR1*]), *PROLINE-RICH EXTENSIN-LIKE RECEPTOR KINASE1* [*PERK1*], *RESISTANCE
634 TO FUSARIUM OXYSPORUM1* [*RFO1*], *FLG22-INDUCED RECEPTOR-LIKE KINASE1*
635 [*FRK1*], and *HERCULES RECEPTOR KINASE1* [*HERK1*].

636

637

638

639 **Supplemental Data**

640 **Supplemental Figure 1.** Comparison of transposable elements number in core regions and
641 accessory regions of Fo47 and Fo5176.

642 **Supplementary Figure 2.** Co-expression gene clusters.

643 **Supplemental Figure 3.** Reciprocal DEGs in endophyte or pathogen infected Arabidopsis plants
644 at each time point.

645 **Supplemental Figure 4.** Expression pattern of key genetic components involved in nitrogen
646 metabolism.

647 **Supplemental Figure 5.** Expression profiles of *in planta*-induced lineage-specific genes for
648 Fo47 and Fo5176, carrying the PFAM domains enriched on fungal accessory chromosomes.

649 **Supplemental Figure 6.** Comparison of the PF03707 domain (regulator of G-protein signaling
650 domain) between Fo47 and Fo5176, and among other filamentous fungi.

651 **Supplemental Figure 7.** Comparison of the PF00188 domain (cysteine-rich secretory protein
652 (CAP) superfamily) between Fo47 and Fo5176, and among other filamentous fungi.

653 **Supplemental Figure 8.** Single-copy orthologs of Fo47 and Fo5176 display conservation and
654 divergence of gene induction during plant infection compared to axenic control.

655 **Supplemental Data Set 1.** PFAM domain enrichment of genes located on accessory
656 chromosomes in Fo47.

657 **Supplemental Data Set 2.** PFAM domain enrichment of genes located on accessory
658 chromosomes in Fo5176.

659 **Supplemental Data Set 3.** Statistics and gene list of 24 co-expression gene clusters.

660 **Supplemental Data Set 4.** Host genes that are preferentially upregulated by Fo47 at 12 HPI.

661 **Supplemental Data Set 5.** Host genes that are preferentially downregulated by Fo47 at 12 HPI.

662 **Supplemental Data Set 6.** Host genes that are preferentially upregulated by Fo5176 at 12 HPI.

663 **Supplemental Data Set 7.** Host genes that are preferentially upregulated by Fo47 at 12 HPI.

664 **Supplemental Data Set 8.** Cluster assignment and annotation of nitrate response genes that were
665 differentially expressed in our study.

666 **Supplemental Data Set 9.** Cluster assignment and annotation of transcription factors that
667 control transcriptional regulation of nitrogen-associated metabolism and growth.

668 **Supplemental Data Set 10.** Overlap of PTI-responsive genes with immunity clusters.

669 **Supplemental Data Set 11.** Overlap of ETI-responsive genes with immunity clusters.

670 **Supplemental Data Set 12.** Genes within C15 that are annotated as encoding plastid-localized
671 proteins.

672 **Supplemental Data Set 13.** Cluster assignment of the genes that are involved in immune
673 signaling.

674 **Supplemental Data Set 14.** Cluster assignment and annotation of *RLP/RLK* genes that were
675 differentially expressed in our study.

676 **Supplemental Data Set 15.** Cluster assignment and annotation of *NLR* genes that were
677 differentially expressed in our study.

678 **Supplemental Data Set 16.** The 1,229 genes located on Fo47 accessory chromosomes and their
679 expression at five selected stages.

680 **Supplemental Data Set 17.** The 4,136 genes located on Fo5176 accessory chromosomes and
681 their expression at five selected stages.

682

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688

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700

701 **AUTHOR CONTRIBUTIONS**

702 Project design and oversight: LG, LJM; Providing fungal strains: CS, VE, HCK; Conducting
703 experiments: LG, LZ, GD, AB, KV; data analysis: LG, HLY, HY, BW, LJM; Results
704 interpretation: LG, HLY, LJM; Manuscript writing: LG, HLY, HCK, LJM; Manuscript revision:
705 all authors; Provide funding: LG, LJM. All authors read and approved the manuscript.

706

707 **Competing Financial Interests**

708 The authors declare no competing financial interests.

709

710 **Figure Legends**

711 **Figure 1. Compatible versus incompatible Arabidopsis interaction with an endophytic
712 (Fo47) versus a pathogenic (Fo5176) *F. oxysporum* strain.**

- 713 A. *F. oxysporum* Fo5176 causes typical wilt symptoms on Arabidopsis Col-0 plants, while
714 Fo47-infected and mock-inoculated plants with water do not exhibit any symptoms.
715 Photographs were taken at 7 d post inoculation (DPI), and representative plants are
716 shown.
- 717 B. Micrographs of Arabidopsis roots mock-inoculated with water or infected with Fo47 or
718 Fo5176 at 5 DPI and stained with X-ARA to reveal *F. oxysporum* hyphae. Scale bar
719 represents 1 mm.
- 720 C. Survival analysis assay illustrating the survival rates of Arabidopsis plants mock-
721 inoculated with water or infected with Fo47 or Fo5176 at six time points, from 4 to 28
722 DPI. Ninety plants were assayed per treatment.
- 723 D. Summary of shoot dry biomass of Arabidopsis plants mock-inoculated with water or
724 infected with Fo47 or Fo5176 at 6 DPI. Statistical significance was determined by
725 Kruskal–Wallis and Wilcoxon rank-sum tests. Asterisk indicates statistical significance at
726 $p < 0.001$. Thirty-six plants were assayed per treatment.

727

728 **Figure 2. Comparative genomics reveals unique sets of accessory chromosomes in *F.*
729 *oxysporum* Fo47 and Fo5176.**

730 Synteny of genome assemblies between *F. verticillioides* (*Fv*) and the two selected *F. oxysporum*
731 strains. Track a: distribution of karyotypes of assembled chromosomes; track b, GC density;
732 track c, density of transposable elements (TEs) calculated in 10-kb windows; track d, gene
733 density, calculated in 100-kb windows. Track e shows syntenic blocks. Relationships are shown
734 through linking syntenic block genes (gene number >10) in each genome pair. Core
735 chromosomes can be identified through synteny between *Fv* and each *Fo* strains, whereas
736 accessory chromosomes and regions show no or reduced synteny. Chromosomes 2, 14, and 18
737 and large segments (size > 1 Mb) of chromosomes 4, 10, 11, 13, and 16 in Fo5176 and
738 chromosome 7 in Fo47 show no synteny with the *Fv* genome and are thus identified as accessory
739 regions, characterized by their high TE density and low gene density.

740

741 **Figure 3. Expression profiling of Arabidopsis roots inoculated with an endophytic versus a
742 pathogenic *F. oxysporum* strain.**

- 743 A. Extent of correlation between Arabidopsis differentially expressed genes (DEGs) in
744 Fo47- and Fo5176-infected plants across the different time points at 12, 24, 48, and 96 h
745 post inoculation (HPI). Correlation coefficients (converted to percentages) are scaled to
746 the sizes and colors of the circles.
747 B. Gene Ontology (GO) enrichment of 24 gene clusters from K-means clustering of
748 Arabidopsis DEGs. The color scale of the heatmap represents the significance level of
749 GO enrichment for biological processes related to stimuli response and developmental
750 processes, expressed as $-\text{Log}_{10}(\text{false discovery rate [FDR]})$. Four clusters, C7, C15, C16,
751 and C21, highly enriched for stimuli responses and deprived of developmental regulation,
752 are highlighted in red and defined as immunity clusters.
753

754 **Figure 4. A summary of transcriptomic changes occurring at 12 HPI.**

755 GO enrichment analysis and visualization were performed on four datasets representing up- and
756 down-regulation by Fo47 and Fo5176, respectively. Nodes represent the GO categories with
757 enrichment, while edges exist when two GO categories share the same genes. The nodes labeled
758 in the same color represent the GO terms that belong to a master term as labeled. The size of the
759 nodes is scaled to the number of genes within each GO term in each figure section.

- 760 A. Pathogen suppression: Arabidopsis genes with expression when infected by Fo47 smaller
761 than when infected by Fo5176 and when infected by water ($47 < 5176$ and $47 < \text{mock}$)
762 B. Pathogen induction: $5176 > 47$ and $5176 > \text{mock}$
763 C. Endophyte suppression: $47 < 5176$ and $47 < \text{mock}$
764 D. Endophyte induction: $47 > 5176$ and $47 > \text{mock}$
765

766 **Figure 5. Expression and GO enrichment of immunity gene clusters.**

- 767 A. Expression profile of immunity gene clusters. Color scale indicates the correlation of
768 expression between genes and the cluster centroids. Genes that were removed from the
769 clusters before functional analysis due to the expression correlation with centroid lower
770 than (or equal to) 0.8 are shown in gray. Enrichment of pathogen-associated molecular
771 pattern-triggered immunity (PTI) and effector-triggered immunity (ETI) genes (defined
772 by Dong et al. 2015) is indicated (in all labeled cases, $P < 1E-7$, by Fisher's exact test).
773 Gene number within the four clusters is as follows: C7, 422; C15, 1,290; C16, 615; C21,
774 766.
775 B. GO enrichment analysis of immunity gene clusters for biological processes, molecular
776 functions, and cellular components. Color scale of the heatmap represents the FDR.
777 Stimuli responses, developmental processes (overlapping with Figure 2C), and redundant
778 GO terms were removed.
779

780 **Figure 6. Distinct biological functions for induced AC genes in the endophyte Fo47 and the**
781 **pathogen Fo5176.**

782 Fold enrichment refers to the ratio of the proportion of genes on the accessory
783 chromosomes (ACs) with a specific term over the proportion of genes in the whole
784 genome with a particular term (adjusted p -value < 0.05).

- 785 A. Significantly induced Fo47 accessory genes are represented in five enriched PFAM
786 domains, including regulator of G-protein signaling domain (PF00615), NO-binding
787 membrane sensor involved in signal transduction (PF03707), bZIP transcription factor
788 (PF00170), chromo domain (PF00385), and bromodomain (PF00439) containing

- 789 proteins.
- 790 B. In Fo5176, six PFAM domains are significantly enriched and induced at different stages
- 791 of infection course: cysteine-rich secretory protein family (PF00188), Calpain family
- 792 cysteine protease (PF00648), peptidase M16 (PF16187), poly (ADP-ribose) polymerase
- 793 regulatory domain (PF02877), cyclin C-terminal domain (PF02984), and WGR domain
- 794 (PF05406).
- 795

796 **Figure 7. Model of transcriptomic plasticity in beneficial and antagonistic plant–fungal**
797 **interactions**

798 Molecular response of *Arabidopsis thaliana* plants challenged with an endophyte Fo47 and a
799 pathogen Fo5176, two *Fusarium oxysporum* strains share a core genome of about 46 Mb, in
800 addition to their unique accessory chromosomes. Distinct responding genes depict the
801 transcriptional plasticity, as the pathogenic interaction activates plant stress responses and
802 suppresses plant growth/development-related functions, while the endophyte attenuates host
803 immunity but activates plant nitrogen assimilation. The differences in reprogramming of the
804 plant transcriptome are linked to accessory genes encoded by the two closely related fungal
805 genomes.

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809 **Supplemental Data**

810 **Supplemental Figure 1. Comparison of transposable element numbers in core regions and**
811 **accessory regions of Fo47 (A) and Fo5176 (B).**

812 Bin size = 100 kb. t-tests were performed, and *p*-values are indicated.

813

814 **Supplemental Figure 2. Co-expression gene clusters.**

815 Results of K-means clustering analysis, yielding 24 co-expression gene clusters. Color scale
816 indicates the correlation of expression between genes and the cluster centroids. Genes
817 that were removed from the clusters before further functional analysis due to the
818 expression correlation with centroid lower than (or equal to) 0.8 are shown in gray. X
819 axis, from left to right in each plot, dictate 96 HPI, 48 HPI, 24 HPI, 12 HPI (Fo47),
820 Mock, 12 HPI, 24 HPI, 48 HPI, and 96 HPI (Fo5176).

821

822 **Supplemental Figure 3. Reciprocal DEGs between endophyte- or pathogen-infected**
823 ***Arabidopsis* plants at each time point.**

- 824 A. Diagram of the overall analysis.
- 825 B. Reciprocal *Arabidopsis* DEGs in endophytic or pathogenic *F. oxysporum* infections at
826 FDR < 0.05.
- 827 C. Gene Ontology analysis (plant GO slim terms) of biological processes and molecular
828 functions for preferentially expressed genes in *Arabidopsis* plants infected with Fo47 or
829 Fo5176 at each time point. Color scale of the heatmap represents the FDR.

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831 **Supplemental Figure 4. Expression pattern of key components involved in nitrogen**
832 **metabolism.**

833 Key components of the nitrogen metabolism pathway were extracted from the KEGG database;
834 the corresponding gene expression profile is shown as a heatmap.

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Supplemental Figure 5. Expression profiles of *in planta*-induced lineage-specific genes for Fo47 (A) and Fo5176 (B), encoding carrying the PFAM domains enriched on fungal accessory chromosomes.

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Supplemental Figure 6. Comparison of the PF03707 domain (regulator of G-protein signaling domain) between Fo47 and Fo5176, and other filamentous fungi

- A. Number of proteins with the PF03707 domain and number of genes encoding this domain.
- B. Phylogenetic tree of proteins with the PF03707 domain in Fo47 and Fo5176.

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Supplemental Figure 7. Comparison of the PF00188 domain (cysteine-rich secretory protein (CAP) superfamily) between Fo47 and Fo5176, and other filamentous fungi

- A. Number of proteins with the PF00188 domain and number of genes encoding this domain.
- B. Phylogenetic tree of proteins with the PF00188 domain in Fo47 and Fo5176.

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Supplementary Figure 8. Single-copy orthologs of Fo47 and Fo5176 display conservation of gene expression.

There were 11,896 orthologs (1:1) between Fo47 and Fo5176. The Pearson correlation coefficient of Fo47 and Fo5176 ortholog expression is 0.73 (mycelia), 0.82 (12 HPI), 0.72 (24 HPI), 0.88 (48 HPI), and 0.92 (96 HPI).

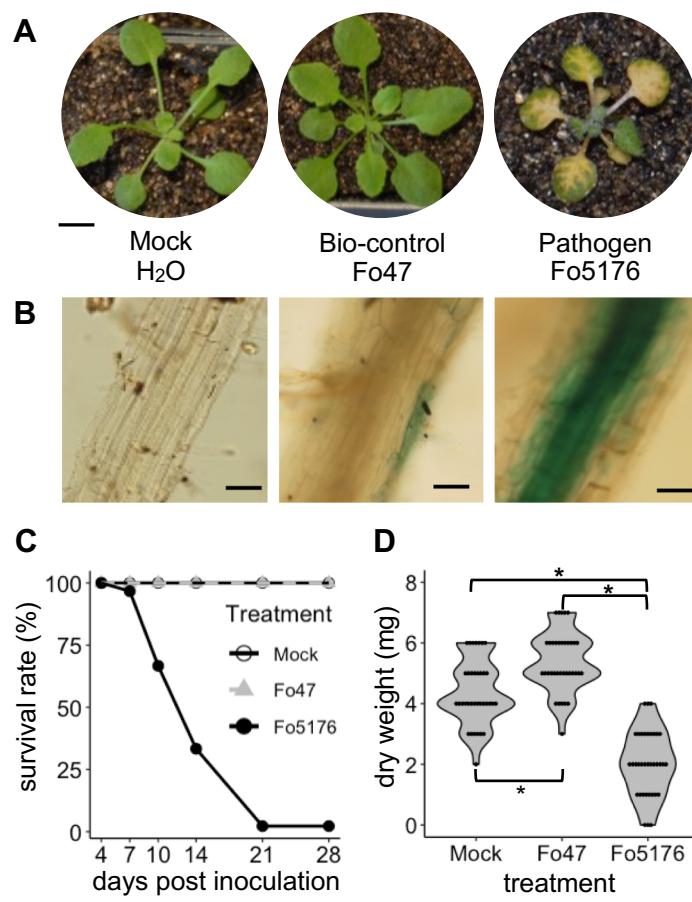


Figure 1. Compatible vs. incompatible *Arabidopsis* interaction with an endophytic (Fo47) versus a pathogenic (Fo5176) *F. oxysporum* strain.

- F. oxysporum* Fo5176 causes typical wilt symptoms on *Arabidopsis* Col-0 plants, while Fo47-infected and mock-inoculated plants with water do not exhibit any symptoms. Photographs were taken at 6 d post inoculation (DPI), and representative plants are shown.
- Micrographs of *Arabidopsis* roots mock-inoculated with water or infected with Fo47 or Fo5176 at 5 DPI and stained with X-ARA to reveal *F. oxysporum* hyphae. Scale bar represents 1 mm.
- Survival analysis assay illustrating the survival rates of *Arabidopsis* plants mock-inoculated with water, or infected with Fo47 or Fo5176 at six time points, from 4 to 28 DPI. 90 plants were assayed per treatment.
- Summary of shoot dry biomass of *Arabidopsis* plants mock-inoculated with water, or infected with Fo47 or Fo5176 at 6 DPI. Statistical significance was determined by Kruskal–Wallis and Wilcoxon rank-sum tests. Asterisk indicates statistical significance at $p < 0.001$. 36 plants were assayed per treatment.

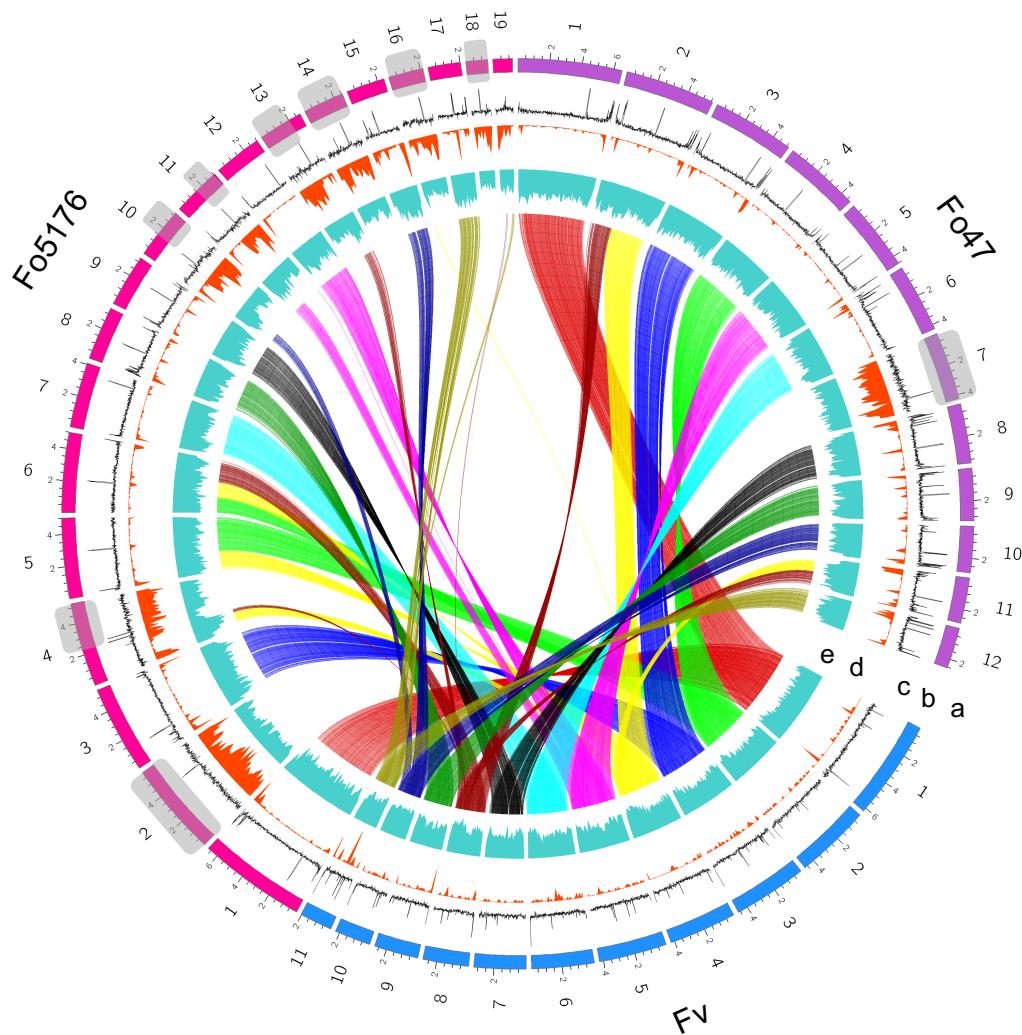


Figure 2. Comparative genomics reveals unique sets of accessory chromosomes in *F. oxysporum* Fo47 and Fo5176, respectively.

Synteny of genome assemblies between *F. verticillioides* (*Fv*) and the two selected *F. oxysporum* strains. Track a: distribution of karyotypes of assembled chromosomes; track b, GC density; track c, density of transposable elements (TEs) calculated in 10-kb windows; track d, gene density, calculated in 100-kb windows. Track e shows syntenic blocks. Relationships are shown through linking syntenic block genes (gene number >10) in each genome pair. Core chromosomes can be identified through synteny between *Fv* and each *Fo* strains, whereas accessory chromosomes and regions show no or reduced synteny. Chromosomes 2, 14, and 18 and large segments (size > 1 Mb) of chromosomes 4, 10, 11, 13, and 16 in Fo5176, and chromosome 7 in Fo47 show no synteny with the *Fv* genome and are thus identified as accessory regions, are characterized by their high TE density and low gene density.

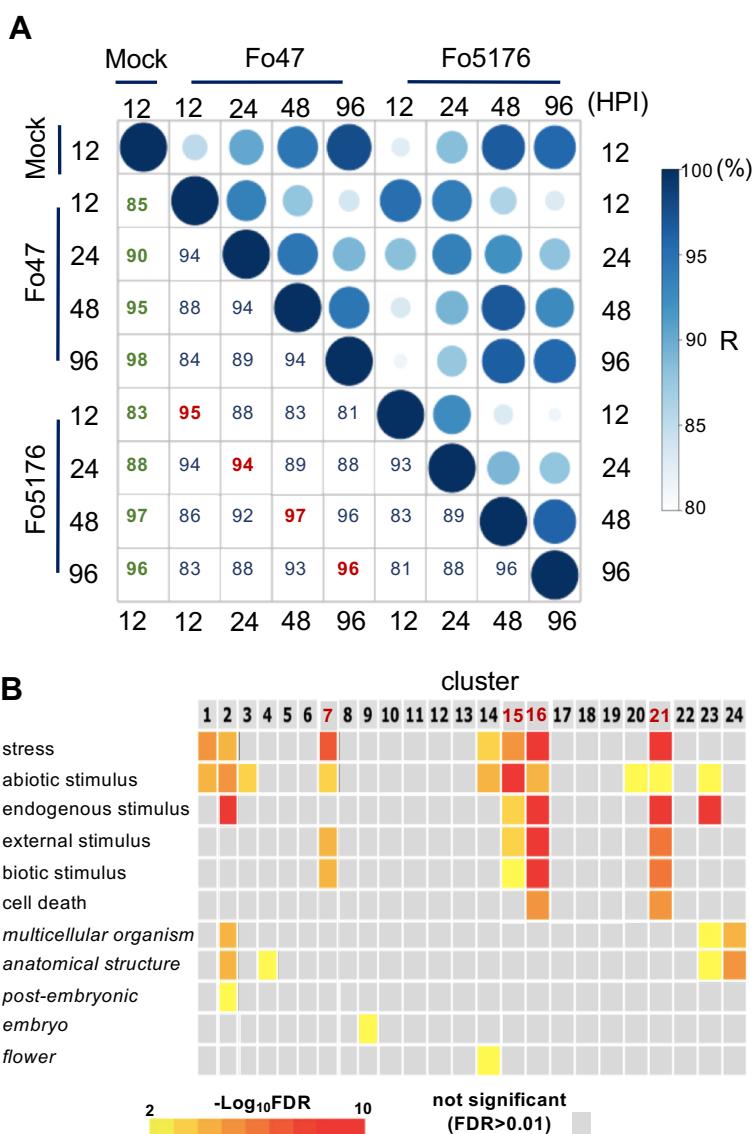


Figure 3. Expression profiling of *Arabidopsis* roots inoculated with an endophytic versus a pathogenic *F. oxysporum* strain.

- A. Extent of correlation between *Arabidopsis* differentially expressed genes (DEGs) in Fo47- and Fo5176- infected plants across the different time points at 12, 24, 48 and 96 h post inoculation (HPI). Correlation coefficients (converted to percentages) are scaled to the sizes and colors of the circles.
- B. Gene Ontology (GO) enrichment of 24 gene clusters from K-means clustering of *Arabidopsis* DEGs. The color scale of the heatmap represents the significance level of GO enrichment for biological processes related to stimuli response and developmental processes, expressed as $-\log_{10}$ (false discovery rate [FDR]). Four clusters, C7, C15, C16, and C21, highly enriched for stimuli responses and deprived of developmental regulation, are highlighted in red and defined as immunity clusters.

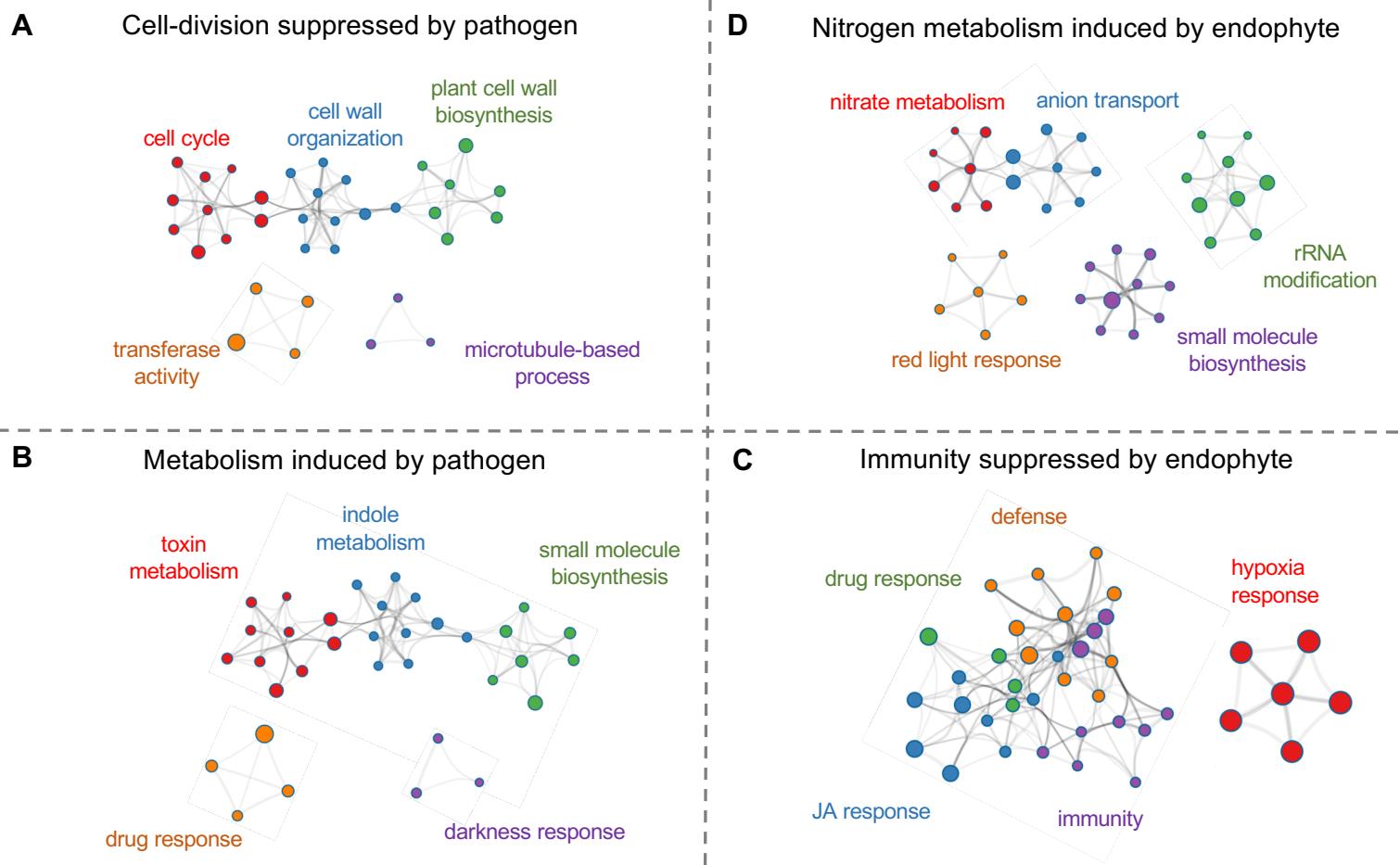


Figure 4. A summary of transcriptomic changes occurring at 12 HPI.

GO enrichment analysis and visualization were performed on four datasets representing up- and down-regulation by Fo47 and Fo5176 respectively. Nodes represent the GO categories with enrichment, while edges exist when two GO categories share the same genes. The nodes labeled in the same color represent the GO terms that belong to a master term as labeled. The size of the nodes is scaled to the number of genes within each GO terms in each figure section.

- Pathogen suppression: Arabidopsis genes with expression when infected by Fo47 smaller than when infected by Fo5176 and when infected by water (47 < 5176 & 47 < mock)
- Pathogen induction: 5176 > 47 & 5176 > mock
- Endophyte suppression: 47 < 5176 & 47 < mock
- Endophyte induction: 47 > 5176 & 47 > mock

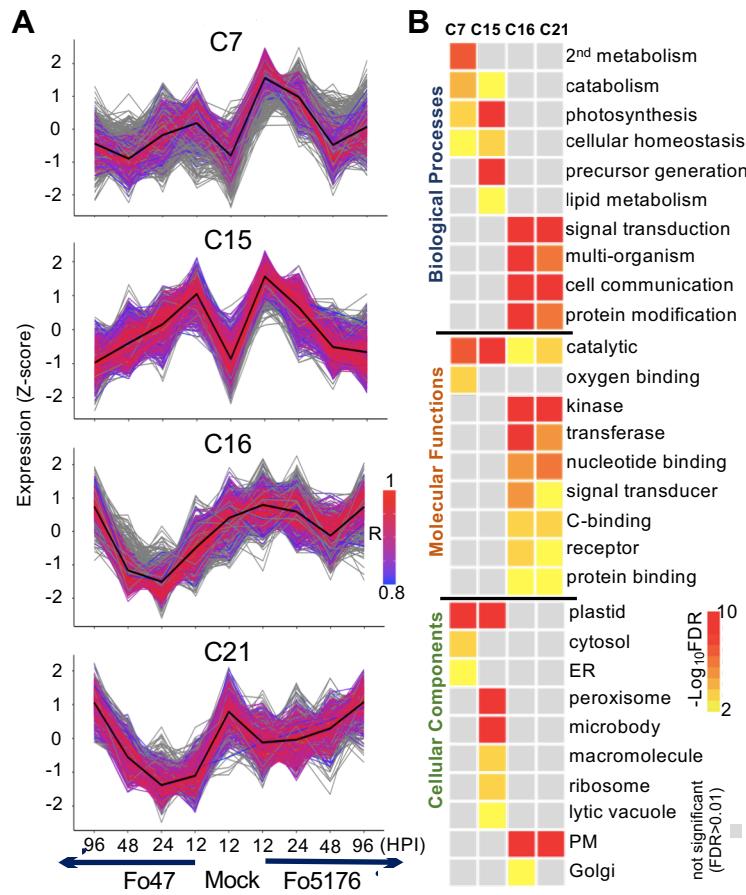


Figure 5. Expression and GO enrichment of immunity gene clusters.

- A. Expression profile of immunity gene clusters. Color scale indicates the correlation of expression between genes and the cluster centroids. Genes that were removed from the clusters before functional analysis due to the expression correlation with centroid lower than (or equal to) 0.8 are shown in gray. Enrichment of pathogen-associated molecular patterns-triggered immunity (PTI) and effector-triggered immunity (ETI) genes (defined by Dong et al. 2015) is indicated (in all labeled cases, $P < 1E-7$, by Fisher's exact test). Gene number within the four clusters is: C7, 422; C15, 1,290; C16, 615; C21, 766.
- B. GO enrichment analysis of immunity gene clusters for biological processes, molecular functions, and cellular components. Color scale of the heatmap represents the FDR. Stimuli responses, developmental processes (overlapping with Figure 2C) and redundant GO terms were removed.

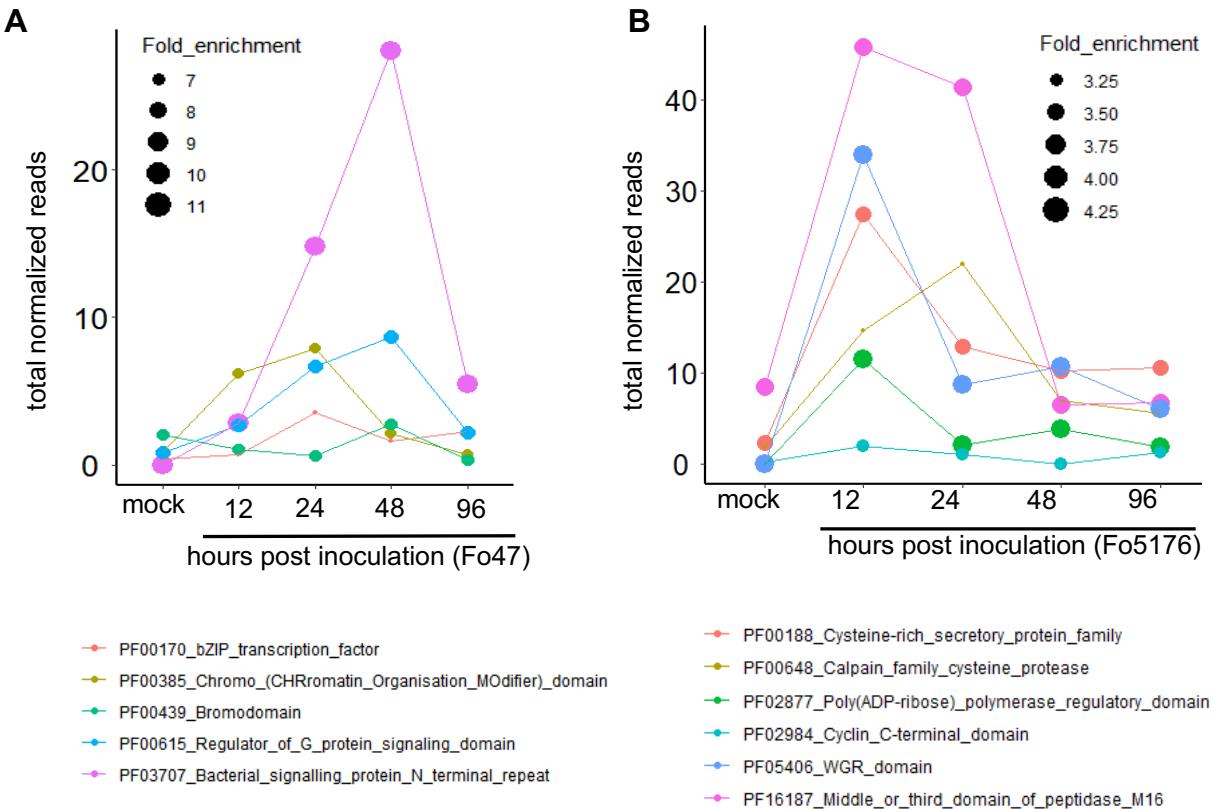


Figure 6. Distinct biological functions for induced AC genes in the endophyte Fo47 and the pathogen Fo5176.

Fold enrichment refers to the ratio of the proportion of genes on the accessory chromosomes (ACs) with a specific term over the proportion of genes in the whole genome with a particular term (adjusted p-value <0.05).

- Significantly induced Fo47 accessory genes are represented in 5 enriched PFAM domains, including regulator of G-protein signaling domain (PF00615), NO-binding membrane sensor involved in signal transduction (PF03707), bZIP transcription factor (PF00170), chromo domain (PF00385), and bromodomain (PF00439) containing proteins.
- In Fo5176, six PFAM domains are significantly enriched and induced at different stages of infection course: cysteine-rich secretory protein family (PF00188), Calpain family cysteine protease (PF00648), peptidase M16 (PF16187), poly (ADP-ribose) polymerase regulatory domain (PF02877), cyclin C-terminal domain (PF02984) and WGR domain (PF05406).

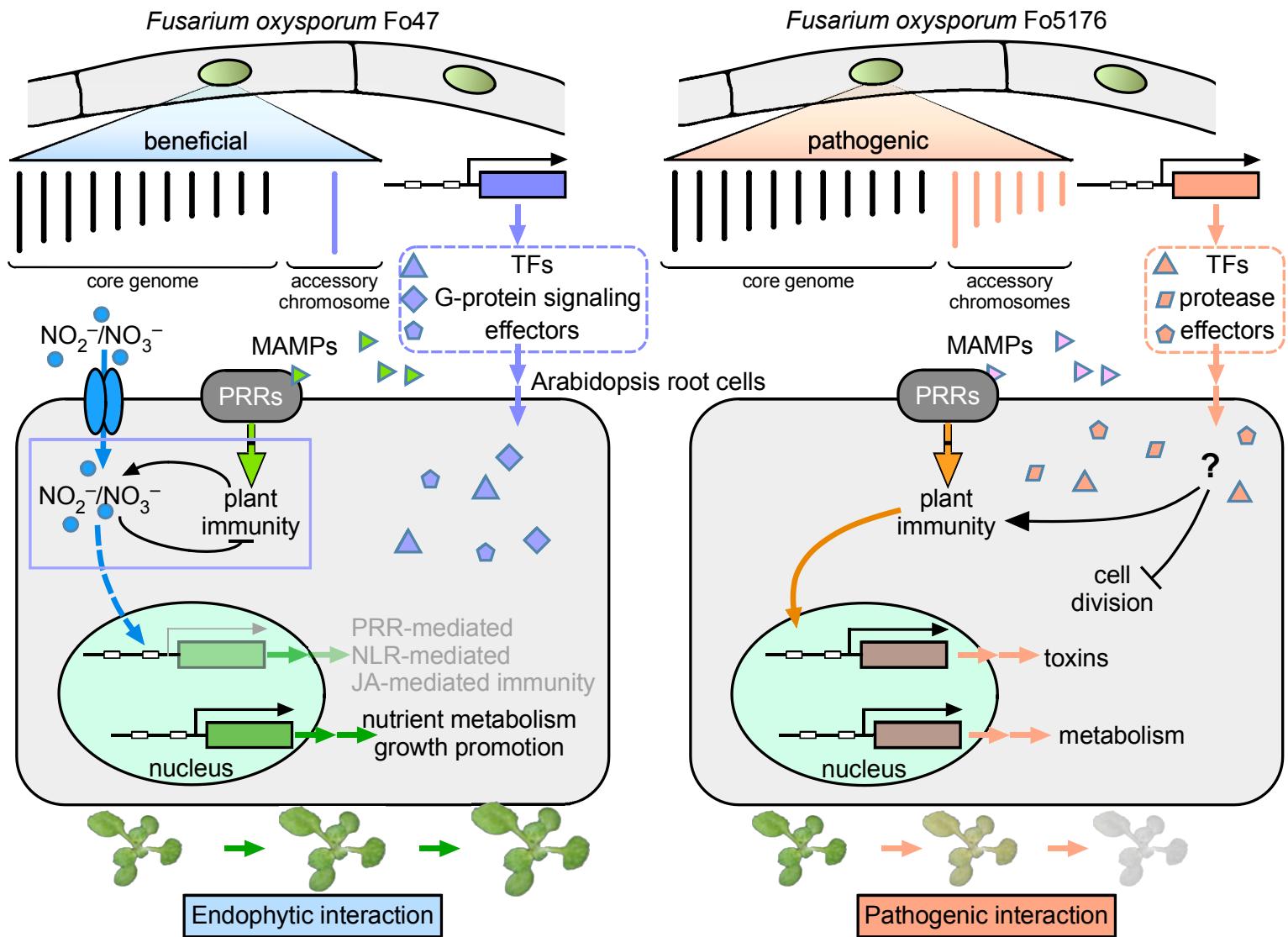


Figure 7. Model of transcriptomic plasticity in beneficial and antagonistic plant-fungal interactions

Molecular response of *Arabidopsis thaliana* plants challenged with an endophyte Fo47 and a pathogen Fo5176, two *Fusarium oxysporum* strains share a core genome of about 46 Mb, in addition to their unique accessory chromosomes. Distinct responding genes depict the transcriptional plasticity, as the pathogenic interaction activates plant stress responses and suppresses plant growth/development related functions; while the endophyte attenuates host immunity, but activates plant nitrogen assimilation. The differences in reprogramming of the plant transcriptome are linked to accessory genes encoded by the two closely related fungal genomes.

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