

## *Trichoderma* Species: Versatile Plant Symbionts

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### ABSTRACT

Because of the need to provide food for the growing population, agricultural activity is faced with the huge challenge of counteracting the negative effects generated by adverse environmental factors and diseases caused by pathogens on crops, while avoiding environmental pollution due to the excessive use of agrochemicals. The exploitation of biological systems that naturally increase plant vigor, preparing them against biotic and abiotic stressors that also promote their growth and productivity represents a useful and viable strategy to help face these challenges. Fungi from the genus *Trichoderma* have been widely used in agriculture as biocontrol agents because of their mycoparasitic capacity and ability to improve plant health and protection against phytopathogens, which makes it an excellent plant symbiont. The mechanisms employed by *Trichoderma* include secretion of effector molecules and secondary metabolites that mediate the beneficial interaction of *Trichoderma* with plants, providing tolerance to biotic and abiotic stresses. Here we discuss the most recent advances in understanding the mechanisms employed by this opportunistic plant symbiont as biocontrol agent and plant growth promoter. In addition, through genome mining we approached a less explored factor that *Trichoderma* could be using to become successful plant symbionts, the production of phytohormones—auxins, cytokinins, abscisic acid, gibberellins, among others. This approach allowed us to detect sets of genes encoding proteins potentially involved in phytohormone biosynthesis and signaling. We discuss the implications of these findings in the physiology of the fungus and in the establishment of its interaction with plants.

The world population is approaching 8 billion people, which imposes on us the challenge of ensuring food provision and energy resources, both of which depend on plants. Moreover, it has been estimated that by 2050 the world's population will swell to 9.7 billion. We will need to increase food production by 50 to 100% for the expected world's population while facing another major challenge, climate change, which is predicted to increase the scale and frequency of emerging plant diseases. In this scenario, it is evident that we require more sustainable agricultural systems that allow significant yield increases and improved quality, while reducing the negative impact of agrochemicals on the environment.

An attractive alternative to secure food production is the use of plant–growth promoting microorganisms. The beneficial effects of microbes on plants depend on complex chemical signaling processes affected by soil type, nutritional state, and climate factors (López-Bucio et al. 2015). In this regard, plant roots release a

number of compounds that affect composition of the microbiota present in the rhizosphere, leading to the establishment of the interactions (Ortiz-Castro et al. 2009). Such symbioses involve plant growth promoting bacteria and fungi, considered natural biostimulants.

Beneficial plant–microbe associations result in more effective nutrient uptake, improved growth and development, and frequently higher tolerance to biotic and abiotic stress (Schirawski and Perlin 2018; Stringlis et al. 2018). Therefore, they help increase crop growth and yield. In addition, plant growth promoting microorganisms are capable of inducing plant defense systems (Jayaraman et al. 2014).

Microorganisms improve plant nutrient uptake, as in the case of mycorrhiza (Plett et al. 2014) or nodule forming bacteria (Igíehon and Babalola 2018), improving plant growth and development (Behie and Bidochka 2014; Igíehon and Babalola 2018). Non-mycorrhizal fungi like *Metarhizium anisopliae* can also improve nitrogen uptake by the plant, mobilizing nitrogen from the insect it parasitizes to the plant roots, resulting in increased nitrogen availability (Behie et al. 2012).

Beneficial microbes can also act as biocontrol organisms, helping plants defend themselves from attack by pathogens. This is the case for fungi of the genus *Trichoderma*, which are excellent mycoparasites of plant pathogens, directly protecting plants against them (Benítez et al. 2004). In addition, *Trichoderma* spp. can also enhance

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the plant defense system through priming, enabling the plant to respond in a much faster and stronger manner to pathogen attack (Beckers et al. 2009; Hermosa et al. 2012; Malmierca et al. 2015). This implies, beneficial microbes can modulate the plant defense system to enable the interaction (Hassani et al. 2018; Jayaraman et al. 2014), like pathogens do through manipulation of the salicylic acid (SA) and/or jasmonic acid (JA) pathways (Berens et al. 2017; Genre and Russo 2016). Not only can manipulation of the JA and SA pathways help establishment of the interaction, but also phytohormones such as auxins, cytokinins (CKs), ethylene (Et), abscisic acid (ABA), and gibberellins (GAs) modulate the relationship between the plant and the beneficial microbe (Van der Ent et al. 2009; Zamioudis and Pieterse 2012). Hormonal modulation is implicated not only in plant defense and beneficial interactions, but in general it controls plant growth and development. Plants require a fine-tuned hormonal balance to grow, develop, reproduce and deal with biotic and abiotic stresses.

Organisms other than plants, particularly soil bacteria and some fungi, have the capacity to produce auxins, CKs, GAs, ABA, and Et. The possible biological role, biosynthesis and applications of fungal phytohormones has been thoroughly reviewed by Tudzynski and Sharon (2002), and more recently by Chanclud and Morel (2016). These authors propose that the hormones could be involved in growth, hyphal or haustoria development, or conidial germination, and that they could also be important during interaction with plants, and not necessarily related to fungus–plant interactions, as some of these hormones are also produced by fungi that are not known to interact with plants (Chanclud and Morel 2016).

*Trichoderma* species have adapted to a plethora of ecosystems, where they play a major role in ecosystem health. These fungi are frequently predominant components of the mycoflora in native and agricultural soils, colonize plant roots, in some cases aerial parts of the plant and can even grow as endophytes. Nevertheless, the commercial success of *Trichoderma* species, with more than 60% of registered biopesticides based on formulations containing at least one strain of the genus is based on their capacity as necrotrophic mycoparasites that sense, invade, and destroy other fungi (Mukherjee et al. 2013). Furthermore, fungi belonging to the genus *Trichoderma* are well known for their capacity to stimulate plant growth and development, as well as their ability to increase plant tolerance to abiotic and biotic stress (López-Bucio et al. 2015). Here we discuss the most recent advances in understanding the mechanisms employed by these

opportunistic plant symbionts as biocontrol agents and plant growth promoters.

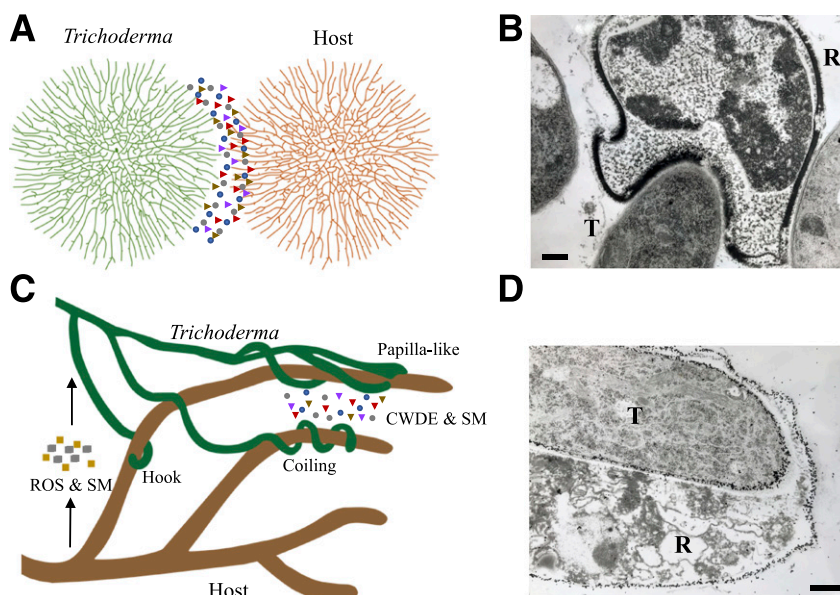
## MYCOPARASITISM BY *TRICHODERMA*

The mycoparasitic interaction of *Trichoderma* with other filamentous fungi is apparently programmed by host signals (Mukherjee et al. 2013), resulting in the production of infective structures and enzyme secretion (Fig. 1). In vitro, the first detectable interaction between *Trichoderma* and its host is the chemotropic growth of the hyphae of the mycoparasite toward its prey, which is likely a response to diffusible signals such as oligochitins (Chet et al. 1981; Cortes et al. 1998). Once the mycoparasite reaches the host, its hyphae often coil around it or attach to it by forming hook-like structures (Fig. 1). Several decades ago, it was proposed that penetration of the host mycelium takes place by partial degradation of its cell wall (Elad et al. 1983). Later, it was proven that indeed, *Trichoderma* secretes a complex set of membrane and cell wall degrading enzymes (CWDEs) (Carsolio et al. 1994; Geremia et al. 1993; Vázquez-Garcidueñas et al. 1998). Those observations, eventually, led to the identification of the first mycoparasitism-related genes, which respond transcriptionally to the presence of a fungal prey (Carsolio et al. 1994; Geremia et al. 1993). Most mycoparasitism-related genes described so far encode CWDEs, which are considered to act synergistically with secondary metabolites and proposed to be determinant in the antagonistic capacity of *Trichoderma* (Schirmböck et al. 1994).

The genome sequences of three species of the genus revealed the richness of genes encoding secondary metabolite biosynthesis pathways and CWDEs required to kill a prey or defend from it (Kubicek et al. 2011). At a genomic scale, the necessity to degrade the prey's cell wall is reflected in the abundance of chitinase and  $\beta$ -1,3-glucanase encoding genes present in the *Trichoderma* genome compared with other fungi (Kubicek et al. 2011). The family of enzymes involved in chitin degradation is strongly expanded in *Trichoderma*, particularly in *T. virens* and *T. atroviride*, which contain the highest number of genes encoding chitinolytic enzymes of all described fungal genomes (Kubicek et al. 2011). In fact, a recent phylogenomic analysis of hypocrealean fungi (including nine *Trichoderma* spp.) revealed that the genus *Trichoderma* likely evolved from an ancestor that fed on either fungi or arthropods. The analysis revealed that the monophyletic family Hypocreaceae, shared a last common ancestor with entomoparasitic

**FIGURE 1**

Mycoparasitism by *Trichoderma*. **A**, Diagram representing the initial steps (before contact) of the interaction between colonies of *Trichoderma* and a fungal prey. **C**, Diagram describing the main factors and structures used by *Trichoderma* and its preys during their antagonistic interaction. ROS, reactive oxygen species; CWDE, cell wall degrading enzymes; and SM, secondary metabolites. **B and D**, Host invasion. Transmission electron micrographs of *T. atroviride* parasitizing *Rhizoctonia solani*. Scale bar 500 nm. **B**, *T. atroviride* (T) penetrates *R. solani* (R). **D**, *T. atroviride* (T) grows inside *R. solani* (R) hypha.



fungi (Druzhinina et al. 2018). Interestingly, mycoparasitism by *Trichoderma* shows very important parallels to insect pathogenicity by species of *Metarhizium*, perhaps the best understood group of entomopathogenic fungi, in terms of signals leading to the production of CWDEs, the battery of enzymes they produce, and the regulation of their expression (Geremia et al. 1993; Carsolio et al. 1994; Freimoser et al. 2005; Hu and St. Leger 2004). Furthermore, it was recently discovered that as in the case of *Trichoderma*, some species of *Metarhizium* are rhizosphere competent and establish beneficial interactions with plants (Behie et al. 2012; Khan et al. 2012; Sasan and Bidochka 2013).

Another class of genes relevant to mycoparasitism are those involved in the synthesis of secondary metabolites, processes for which at least three of the *Trichoderma* genomes sequenced (*T. atroviride*, *T. reesei*, and *T. virens*) contain a varying assortment of genes coding for nonribosomal peptide synthetases (NRPS) and polyketide synthases (PKS). *T. virens* contains the highest number of NRPS (28), compared with 19 and 16 in its closest competitors *Fusarium graminearum* and *T. atroviride*, respectively. Interestingly, half of the secondary metabolite gene clusters present in *T. virens* and *T. atroviride*, considered effective mycoparasites, are not present in the *T. reesei* genome (Kubicek et al. 2011).

The advent of genomic technologies fostered genome wide gene expression analyses. In this regard, an EST-based analysis of gene expression during the interaction of *T. atroviride* with *Botrytis cinerea*/*Rhizoctonia solani* allowed the identification of 66 genes that were overexpressed during the onset of mycoparasitism (Seidl et al. 2009). The most abundant genes were involved in post-translational processing and amino acid metabolism and included components of the stress response reaction to nitrogen shortage, signal transduction and lipid catabolism. Interestingly, in that analysis only a few genes encoding CWDEs were up-regulated during the early stages of mycoparasitism. Two of them encoded proteases, which was interpreted as indicating a possible major involvement of proteases in the first stages of mycoparasitism as key factors liberating molecules that would signal the presence of a fungal prey.

Using a high-throughput transcriptome analysis, 175 genes from *T. atroviride* were identified that responded to the presence of *R. solani*. In agreement with the observations made by Seidl and coworkers (2009), functional annotation of the responsive genes indicated that the most abundant group of genes up-regulated during direct contact with the prey was metabolism. Further analysis confirmed that 13 genes tested, including those encoding an expansin-like protein (*swol*), acetyl xylan esterase (*axeI*), aspartyl protease (*papA*), and a trypsin-like protease (*pra1*) are indeed up-regulated in response to the presence of *R. solani* (Reithner et al. 2011).

A comparative transcriptomic analysis of *T. atroviride*, *T. virens*, and *T. reesei* revealed a strikingly different response prior to physical contact with the host hyphae. *T. atroviride* expressed a set of genes involved in production of secondary metabolites,  $\beta$ -glucanases, various proteases and small secreted cysteine rich proteins, while *T. virens* expressed the genes necessary for gliotoxin biosynthesis. Interestingly, *T. reesei* increased the expression of genes involved in cellulose degradation (Atanasova et al. 2013). Thus, the weapons used by different *Trichoderma* species and even isolates are different, which may be used as a major feature for the development of biofungicides.

## TRICHODERMA-PLANT INTERACTIONS

*Trichoderma* improves plant growth and development in axenic conditions but also in the field on a variety of crops (Hermosa et al. 2012; Mukherjee et al. 2013). In this regard, the fungal mycelium secretes compounds that promote root branching, thus improving nutrient and water acquisition (Garnica-Vergara et al. 2016). In addition, *Trichoderma* species can modulate the plant defense

systems, interacting with the different signaling pathways involved. It is well understood that modulation of the SA pathway enables the establishment of the interaction between *T. harzianum* and *A. thaliana*, where SA restricts the amount of colonized root tissue by *T. harzianum* (Alonso-Ramírez et al. 2014). Nonetheless, fungi like *T. atroviride* can finely modulate both SA and JA pathways to promote resistance (Salas-Marina et al. 2011).

Communication between *Trichoderma* and plants involves secreted proteins as key factors, as it has been observed in plant-pathogen/mycorrhizae interactions. Recent analyses have shown that the *Trichoderma* genomes encode hundreds of potential effector proteins (Guzmán-Guzmán et al. 2017; Mendoza-Mendoza et al. 2018; Nogueira-López et al. 2018). In a few cases, the role of effectors in the establishment of the *Trichoderma*-root association has been experimentally demonstrated. Protein profiles, determined from maize root tissue in interaction with *T. virens* show that, in addition to effectors, *T. virens* secretes products related to secondary metabolism, that help the fungus in scavenging reactive oxygen species and hydrolysis of the plant cell wall (Nogueira-López et al. 2018).

From the predicted secretome, we demonstrated the differential expression of genes with predicted functions corresponding to different families during the *Trichoderma*-plant interaction. Among them *tatr2* from *T. atroviride*, which encodes a thioredoxin. Thioredoxins play important roles as effectors, inhibiting apoptotic processes mediated by stress-activated MAPK signaling cascades (Lee et al. 2005; Rivas et al. 2004). *tatr2* could play a role in mediating the beneficial interaction between *Arabidopsis* and *T. atroviride*, inducing plant resistance. We also found differential expression of the *T. atroviride* *tacfm1* gene, encoding a CFEM (common in fungal extracellular membrane) protein; these proteins are involved in appressorium formation in *Magnaporthe oryzae*, previously known as *Magnaporthe grisea* (Kulkarni et al. 2003). The *tvlysm1* and *talysm1* genes of *T. virens* and *T. atroviride*, respectively, encoding members of the LysM repeats family, were also differentially expressed during the *Trichoderma*-*Arabidopsis* interaction. LysM proteins play roles in pathogenic systems binding chitin oligomers from the fungus, avoiding recognition by the plant and favoring colonization (De Jonge and Thomma 2009), so that in *Trichoderma* they could increase its plant association capacity. Finally, *tvhdi1*, encoding a class II hydrophobin from *T. virens*, is involved in the plant colonization process (Guzmán-Guzmán et al. 2017).

Another interesting possibility that could explain how *Trichoderma* manipulates the plant is through the production of phytohormones. Therefore, for this review, we searched among the *T. atroviride* genome for genes that could participate in the biosynthesis and signaling of molecules like SA or JA, and other phytohormones. We used as seed the *A. thaliana* protein sequences involved in biosynthesis and signaling of the SA, JA, auxins, CKs, GAs, Et, and ABA pathway in BLASTP against the database of the *T. atroviride* genome (v.2.0). Coupled to this approach, we selected some of the sequences that showed the highest percentage of similarity for each protein and, performed BLASTP against the genomes of the basal plants *Physcomitrella patens* and *Marchantia polymorpha*. Similarly, we performed BLASTP analyses using fungal and bacterial proteins, which function in phytohormone synthesis is supported by experimental evidence (Table 1). Interestingly, the only pathway for which we found no orthologs was that involved in JA biosynthesis.

## PRIMING OF PLANT DEFENSE RESPONSES

The molecular basis of systemic resistance (ISR) induced by *T. hamatum* in *A. thaliana* has been analyzed by microarrays. Treatment with *T. hamatum* accelerated activation of the defense response against *B. cinerea*, which was interpreted as ISR-boost,



and confirmed using mutants affected in various defense-related pathways (Mathys et al. 2012). Similarly, Morán-Díez et al. (2012) analyzed *A. thaliana* gene expression changes when exposed to *T. harzianum*, they detected changes in genes related to both biotic and abiotic stress responses, involving several signal transduction pathways controlled by phytohormones. Their data support the hypothesis that SA- and JA-related genes were downregulated in *A. thaliana* in the presence of *T. harzianum*, while several genes related to abiotic stress responses were upregulated. Accordingly, they hypothesized that at an early stage of the interaction the plant defenses mediated by JA and SA are reduced, allowing root colonization. Thus, *Trichoderma* was not perceived as a threat by the host plant, while upon longer exposure to *Trichoderma* defense responses would be activated both locally and systemically.

Given that effector proteins could be responsible for the activation of the plant defense response, the role of some of them has been examined in detail. The *T. virens* hydrophobin-like protein Sm1 induces systemic disease resistance in cotton and maize against *Colletotrichum* spp., while its *T. atroviride* ortholog (Epl1), confers protection in tomato plants against *A. solani* and *B. cinerea*. This protection correlates with the expression of genes associated with the JA defense response, or with those genes encoding enzymes with peroxidase and an  $\alpha$ -dioxygenase activity (Djonovic et al. 2007; Salas-Marina et al. 2015). In addition to Sm1 and Epl1, their paralogs Sm2 and Epl2, seem to be important for the *Trichoderma*–maize interaction, enhancing protection and reducing leaf lesion size caused by *Cochliobolus heterostrophus* (Gaderer et al. 2015). Similarly, the hydrophobin HYTL01 from *T. longibrachiatum* induces the expression of genes related to the SA- and JA-mediated defense pathways, enhancing protection in tomato and pepper against *B. cinerea* (Ruocco et al. 2015), and the *T. asperellum* swollenin TasSwo induces the expression of defense-related genes in cucumber plants (Brotman et al. 2008).

Some other *Trichoderma* nonproteinaceous molecules have the capacity to induce plant defense systems. The secondary metabolite harzianolide from *T. harzianum*, increased the expression of marker genes related to both JA/Et- and SA-mediated defense pathways in tomato (Cai et al. 2013).

Effector proteins and secondary metabolites are thus thought to be relevant in the establishment of the *Trichoderma*–plant symbiosis, and in triggering plant defense responses by activating the production of SA and/or JA. Nevertheless, it is possible that in addition to the release of protein effectors, *Trichoderma* might directly deliver these signaling molecules.

**Salicylic acid.** Salicylic acid (SA) is a small phenolic compound involved in many plant physiological processes; it functions as a signal molecule during plant defense, mediating one of the major defenses against biotrophic fungi. In plants, there are two SA biosynthesis pathways: the isochorismate pathway (IC), and the phenylpropanoid pathway (PAL), both pathways initiate with chorismate as precursor, which is the final product of the shikimate pathway (Seyfferth and Tsuda 2014). IC synthase (ICS or SID2) is a key enzyme that catalyzes the first step of the IC pathway, converting chorismate into isochorismate; while PAL is the enzyme that catalyzes the first step in the phenylpropanoid pathway, converting phenylalanine into cinnamic acid (Seyfferth and Tsuda 2014). We found two genes in the *T. atroviride* genome encoding enzymes with putative phenylalanine ammonia-lyase (ID 260476) and isochorismate synthase activity (ID 297768) (Table 1). According to our search, *T. atroviride* could synthesize SA, through either the PAL and/or the IC pathway.

## PLANT GROWTH STIMULATION

The efficacy of *Trichoderma* spp. as biofertilizers has gained support from multiple reports indicating that when applied to soil,

seeds, or plant surfaces, it increases the solubility of nutrients as well as the nutrient uptake capacity of the root. The beneficial effect of *Trichoderma* on plants can be explained by the capacity of the fungus to modulate root architecture and/or through the production of compounds that increase nutrient availability, such as siderophores and organic acids (reviewed in López-Bucío et al. 2015).

Phytohormones produced by fungi have recently been shown to play important roles in pathogenic fungus–plant interactions. However, information on their participation in beneficial fungus–plant interactions is scarce.

**Auxins.** Auxins are a group of compounds derived from indole that in plants regulate cell division and elongation, and root initiation, to mention some of their biological roles. Some phytopathogenic fungi like *Fusarium* spp., *Rhizoctonia* spp., and *Colletotrichum gloeosporioides* have been identified as auxin producing fungi, primarily affecting spore germination and cell elongation (Chanclud and Morel 2016; Tudzynski and Sharon 2002). In *Phycomyces blakesleeanus*, exogenous application of auxins increased the growth rate of the fungus, and the growing zone of the sporangium, indicating that auxins play a physiological role in this organism (Živanović et al. 2018).

Biosynthesis of auxins in plants is very complex, and is divided in two major types, tryptophan (Trp)-independent and Trp-dependent pathways (Mano and Nemoto 2012). Four pathways have been proposed as Trp-dependent that lead to the biosynthesis of IAA: (i) the YUCCA (YUC); (ii) the indole-3 pyruvic acid (IPA); (iii) the indole-3 acetamide (IAM); and (iv) the indole-3-acetaldoxime (IAOx) pathways (Mano and Nemoto 2012; Mashiguchi et al. 2011). In fungi auxin biosynthesis has been shown to take place through the IAM in *Fusarium* sp. and *C. gloeosporioides*, and the IPA pathway in *Ustilago* sp. and *Rhizoctonia* sp. (Kochar et al. 2011; Chanclud and Morel 2016).

*T. virens* can produce at least two auxin related compounds, indole-3-acetic acid (IAA) and indole-3-acetaldehyde (IAAld), through a Trp-dependent pathway, which led to the proposal that auxin production regulates plant root architecture (Contreras-Cornejo et al. 2009). However, the proposed role of auxins synthesized by the fungus and regulation of root architecture is still in debate (Hoyos-Carvajal et al. 2009; Nieto-Jacobo et al. 2017), since changes in root architecture are also promoted by volatile organic compounds produced by several *Trichoderma* strains (Fig. 2) (Nieto-Jacobo et al. 2017). In fact, there is evidence that the volatile 6-pentyl-2H-pyran-2-one (6-PP) produced by *T. atroviride* provokes changes in root architecture, increasing plant biomass through auxin signaling in *Arabidopsis* (Garnica-Vergara et al. 2016). To determine beyond doubt the role of auxins in the *Trichoderma*–plant interaction, it is essential to test mutants affected in auxin synthesis.

We identified in the *T. atroviride* genome 10 genes with orthologs in *A. thaliana* or *U. maydis* that play a role in auxin biosynthesis or signaling, including genes putatively involved in the IAM and IPA pathways (Table 1). These auxin biosynthesis pathways have been characterized in *Fusarium* and *Ustilago*. In the *Fusarium* sp. genome, Tsavkelova et al. (2012) found a gene cluster with one indole-3-acetamide hydrolase and one tryptophan monooxygenase encoding gene and showed that the IAM pathway is fully functional in *F. proliferatum* ET1. We found two sequences in *T. atroviride* encoding a putative IAM hydrolase (ID 316778 and 30057) and a tryptophan amino transferase (transaminase) (Table 1) (ID 149780). In *U. maydis*, two indole-3-acetaldehyde dehydrogenase genes are involved in IAA production via indole-3-pyruvic acid (Reineke et al. 2008). For this pathway in *T. atroviride* we found one sequence (ID 138587) with its best hit to an *A. thaliana* flavin monooxygenase encoding gene, and one (ID 141294) encoding a protein with putative aldehyde oxidase and xanthine dehydrogenase functions (Table 1). The presence of these sequences in the *T. atroviride* genome suggests that these fungi can synthesize auxins, through the

IPA pathway, as previously reported by Contreras-Cornejo et al. (2009), or via the IAM pathway. Although we found some genes encoding enzymes related to the other two biosynthesis pathways, the pathways appear incomplete.

In *Arabidopsis*, auxin transport is mediated by four main protein families: (i) auxin resistance (AUX1), (ii) pin formed (PIN); (iii) pin-like (PILS); and (iv) ATP-binding cassette B (ABCB) (Feraru et al. 2012; Křeček et al. 2009). Whereas, auxin signaling is mediated by four different protein families: (i) auxin response factor (ARF); (ii) auxin-indole-3-acetic acid (AUX-IAA); (iii) transport inhibitor response-auxin signaling f-box protein (TIR/AFB); and (iv) auxin binding protein 1 (ABP1) (Finet et al. 2013). A BLAST search using *Arabidopsis* auxin-transport genes as query allowed the identification of genes related to auxin transport of the AUX1, PILS, and ABCB families in the *P. blakesleeanus* genome, but none related to the PIN family (Živanović et al. 2018). We found that the *T. atroviride* genome contains three sequences (IDs 297344, 297671, and 146579) with the predicted function of GTP-binding ADP-ribosylation factor

and GTP-binding ADP-ribosylation factor-like protein, related to the *Arabidopsis* ARF3 gene (Table 1). The fact that we found genes involved in auxin biosynthesis and signaling in the *T. atroviride* genome suggests that *Trichoderma* may not only produce auxins, but that the fungus may also be able to perceive them. Thus, auxins could actually play a role in the physiology of the fungus, regardless of its interaction with the plant.

**Cytokinins (CKs).** CKs are hormones involved in plant cell differentiation, root and shoot branching, stress tolerance, and nutrient balance (Müller and Sheen 2007). CKs are important in the establishment of plant–microbe interactions and defense. CKs when applied exogenously to *A. thaliana* induce resistance to the pathogen *Hyaloperonospora arabidopsidis*. Cytokinins may also function as priming agents because when plants are treated with them and no pathogen challenge is presented there is no defense activation, activation only occurs upon pathogen infection (Albrecht and Argueso 2017). Several reviews regarding priming by beneficial fungi indicate a role of various *Trichoderma* species in activating plant defenses (Balmer et al.

**TABLE 1**  
***Trichoderma atroviride* genes putatively involved in phytohormone synthesis and signaling pathways**

Hormone	JGI catalog ID	Molecular function in <i>Trichoderma</i>	% Identity	% Similarity
Auxins	138587	Flavin-containing monooxygenase	32	49
	141294	Aldehyde oxidase and xanthine dehydrogenase, molybdopterin binding	32	49
	316778	Amidase	36	50
	54776	Cytochrome P450, E-class, group I	25	39
	297344	GTP-binding ADP-ribosylation factor Arf1	59	78
	297671	GTP-binding ADP-ribosylation factor-like protein ARL1	60	75
	146579	GTP-binding ADP-ribosylation factor Arf6 (dArf3)	55	75
	30057	Aldehyde dehydrogenase	49	66
	149780	Aromatic amino acid aminotransferase and related proteins	27	44
	154814	Pyruvate decarboxylase/indole pyruvate decarboxylase	25	44
Abscisic acid	158420	Short-chain-dehydrogenase/reductase	37	50
	141294	Aldehyde oxidase, Xanthine oxidase activity	32	49
	80521	Cytochrome P450, E-class, group IV	34	56
	295125	Cytochrome P450, E-class, group I	38	57
	28537	Putative reductases/dehydrogenases with broad range of substrate specificities	45	65
	129592	Cytochrome P450, E-class, group IV	27	43
Gibberellins	160158	Geranylgeranyl pyrophosphate synthase	39	55
	160158	Geranylgeranyl pyrophosphate synthase	35	55
	293815	Cytochrome P450, E-class, group IV	35.4	56
	293815	Cytochrome P450, E-class, group IV	34	51
	156885	Cytochrome P450, E-class, group IV	30.5	50
	302240	Gibberellin oxidase	75	83
	284926	Polyprenyl synthetase	34	47
	143946	Hydroxymethylglutaryl-CoA reductase	73	83
Ethylene	301763	S-adenosylmethionine synthetase	80.5	91
	297477	1-Aminocyclopropane-1-carboxylate synthase	41.3	59
	39146	Iron/ascorbate family oxidoreductases	45.2	55
	238874	1-Aminocyclopropane-1-carboxylate deaminase	95	98
	301763	S-Adenosylmethionine synthetase	61	76
	301763	S-Adenosylmethionine synthetase	61	75
	301802	2OG-Fe(II) oxygenase	35	53
Salicylic acid	260476	Phenylalanine ammonia-lyase	41	60
	297768	Isochorismate synthase	26	44
Cytokinins	278239	tRNA isopentenyltransferase	64	79
	134727	Putative lysine decarboxylase family	40	57
	134727	Possible lysine decarboxylase	42	59
	148265	Protein-histidine kinase activity	32	49
	286374	Protein-histidine kinase activity	39	62
	88129	Two-component response regulatory activity	30	51
	255011	Adenosine kinase activity	43	64

(Continued on next page)

2015; Shores et al. 2010). Nevertheless, in ectomycorrhizal mycelia, CKs promote hyphal branching (Barker and Tagu 2000); and in *M. oryzae*, CKs help the fungus tolerate oxidative stress (Chanclud et al. 2016).

Cytokinin biosynthesis in plants begins with isopentenyl transferase (IPT) or tRNA-IPT, using dimethylallyl-diphosphate (DAMPP) as substrate, being N<sup>6</sup>-(Δ<sup>2</sup>-isopentenyl) adenosine-5'-triphosphate and -diphosphate ribonucleotides (iPRT and iPRDP, respectively) the products of this first step. Later, cytochrome P450 monooxygenases (CYP735A1 and CYP735A2) convert both products to transzeatin ribonucleotides (tZRT and tZRD). Finally, the active CK forms are obtained by the LONELY GUY (LOG) family of enzymes (Simm et al. 2016). In *Magnaporthe oryzae* (Chanclud et al. 2016) and *Claviceps purpurea* (Hinsch et al. 2015), the putative IPT and LOG genes have been characterized, and both fungi are capable of producing CKs.

We identified six genes in *T. atroviride* that in *Arabidopsis*, *Marchantia polymorpha*, or *C. purpurea* are related to CK signaling or biosynthesis. Five of the six genes are related to CK

biosynthesis, with putative, tRNA isopentenyl transferase, LOG or lysine decarboxylase activities (Table 1). Thus, the *T. atroviride* genome encodes the main enzymes required for CK biosynthesis (IDs 278239 and 134727), suggesting that this fungus produces CKs.

In *A. thaliana*, there are at least three receptors involved in plant CKs signaling: histidine kinase 2 (AHK2), histidine kinase 3 (AHK3), and histidine kinase 4 (AHK4/CRE1/WOL) (Hirose et al. 2008). In *T. atroviride* we found two genes (IDs 148265 and 286374) encoding proteins with predicted protein-histidine kinase activity with high similarity to the *Arabidopsis* AHK2 and AHK4 proteins, and other sequences with predicted response regulatory activity (ID 88129) and adenosine kinase activity (ID 255011), similar to the *Arabidopsis* ARR4 and ADHK2 proteins, which are also involved in CKs signaling (Table 1).

One of the sequences related to CK biosynthesis has an ortholog in the genome of *C. purpurea* (Table 1) (ID 278239), which is known to produce CKs (Hinsch et al. 2015). These findings

**TABLE 1**  
(Continued from previous page)

% Coverage	E-value	Target annotation	Best hit
72	4.00E-43	Flavin-containing monooxygenase	<i>Arabidopsis thaliana</i> AT1G04610.1 (YUC3)
97	0.00E+00	Aldehyde oxidase	<i>A. thaliana</i> AT5G20960.1 (AAO1)
42	1.00E-20	Indole-3-acetamide hydrolase	<i>A. thaliana</i> AT1G08980.1 (AUX2/AMI1)
86	5.00E-24	Cytochrome P450, family 79, subfamily B polypeptide 3	<i>A. thaliana</i> AT2G22330.1 (CYP79B3)
97	2.00E-86	Auxin response factor 3	<i>A. thaliana</i> AT2G24765.1 (ARF3)
98	5.00E-83	Auxin response factor 3	<i>A. thaliana</i> AT2G24765.1 (ARF3)
95	2.00E-78	Auxin response factor 3	<i>A. thaliana</i> AT2G24765.1 (ARF3)
97.5	1.00E-169	Indole-3-acetamide hydrolase	<i>Ustilago maydis</i> 23563863
91	7.00E-53	Tryptophan amino transferase (transaminase)	<i>U. maydis</i> 23562703
97	2.00E-45	Indole pyruvate decarboxylase <i>ipdC</i>	<i>AKE79070.1 A. brasiliense</i> Sp245
96	2.00E-44	Short-chain-dehydrogenase/reductase	<i>A. thaliana</i> SDR2 AT3G51680.1
97	0.00E+00	Aldehyde oxidase, Xanthine catabolic process	<i>A. thaliana</i> AAO1 AT5G20960.1
94	8.00E-102	bcaba1	<i>Botrytis cinerea</i> XP_024550391.1
98	3.30E-122	bcaba2	<i>B. cinerea</i> CAH64679.1
97	3.00E-74	bcaba4	<i>B. cinerea</i> CAJ87068.1
80	1.00E-35	cyc	<i>Agrobacterium tumefaciens</i>
88	2.00E-59	Geranylgeranyldiphosphate synthase (ggS2)	<i>Sphaceloma manihoticola</i> CAP07654.1
85	6.00E-65	Geranylgeranyldiphosphate synthase	<i>Fusarium fujikuroi</i> CAA75568.1
85	3.00E-101	Cytochrome P450 monooxygenase 1 (GA14 synthase)	<i>F. fujikuroi</i> XP_023431254.1
88	2.00E-91	Cytochrome P450 monooxygenase 2 (Gibberellin 20-oxidase)	<i>F. fujikuroi</i> XP_023431253.1
98	7.09E-77	Cytochrome P450 monooxygenase 4 (Ent-kaurene oxidase P450-4)	<i>F. fujikuroi</i> XP_023431255.1
98	0.00E+00	Gibberellin oxidase	<i>F. fujikuroi</i> KLO80093.1
97	4.00E-54	Octaprenyl-diphosphate synthase	<i>Pseudomonas fluorescens</i> HK44_026980
99	0.00E+00	HMGO coA reductase	<i>Metarhizium acridium</i> CQMa 102
98.2	0.00E+00	S-Adenosylmethionine synthetase	<i>B. cinerea</i> 5353 (JGI)
80.8	1.10E-60	1-Aminocyclopropane-1-carboxylate synthase	<i>B. cinerea</i> 5135 (JGI)
81.7	2.21E-63	Iron/ascorbate family oxidoreductases	<i>B. cinerea</i> 401 (JGI)
98	0.00E+00	1-Aminocyclopropane-1-carboxylate deaminase (ACC)	<i>Trichoderma asperellum</i> T203
			FJ751936.1
97	7.00E-167	S-Adenosylmethionine synthetase (metK)	Pp3c19_3060
96	1.00E-165	Ethylene biosynthesis I	Pp3c22_12800
95	1.00E-67	2OG-Fe(II) oxygenase	<i>Pseudomonas</i> sp.
			PMM47T1_11647
74	2.00E-118	Phenylalanine ammonia-lyase	Pp3c24_13110
59	1.00E-22	ISC2 isochorismate synthase activity	<i>A. thaliana</i> AT1G18870
99	0.00E+00	Related to tRNA isopentenyltransferase	<i>Claviceps purpurea</i> CCE29200.1
87	4.00E-51	LOG7	<i>A. thaliana</i> AT5G06300
76	8.00E-51	Cytokinin riboside 5'-monophosphate phosphoribohydrolase	<i>Marchantia polymorpha</i>
		LOG3-related	Mapoly0103s0059.1
52	2.00E-74	AHK2	<i>A. thaliana</i> AT5G35750
45	6.00E-27	AHK4	<i>A. thaliana</i> AT2G01830
72	4.00E-10	ARR4	<i>A. thaliana</i> AT1G10470
98	8.00E-102	ADHK2	<i>A. thaliana</i> AT5G03300.1

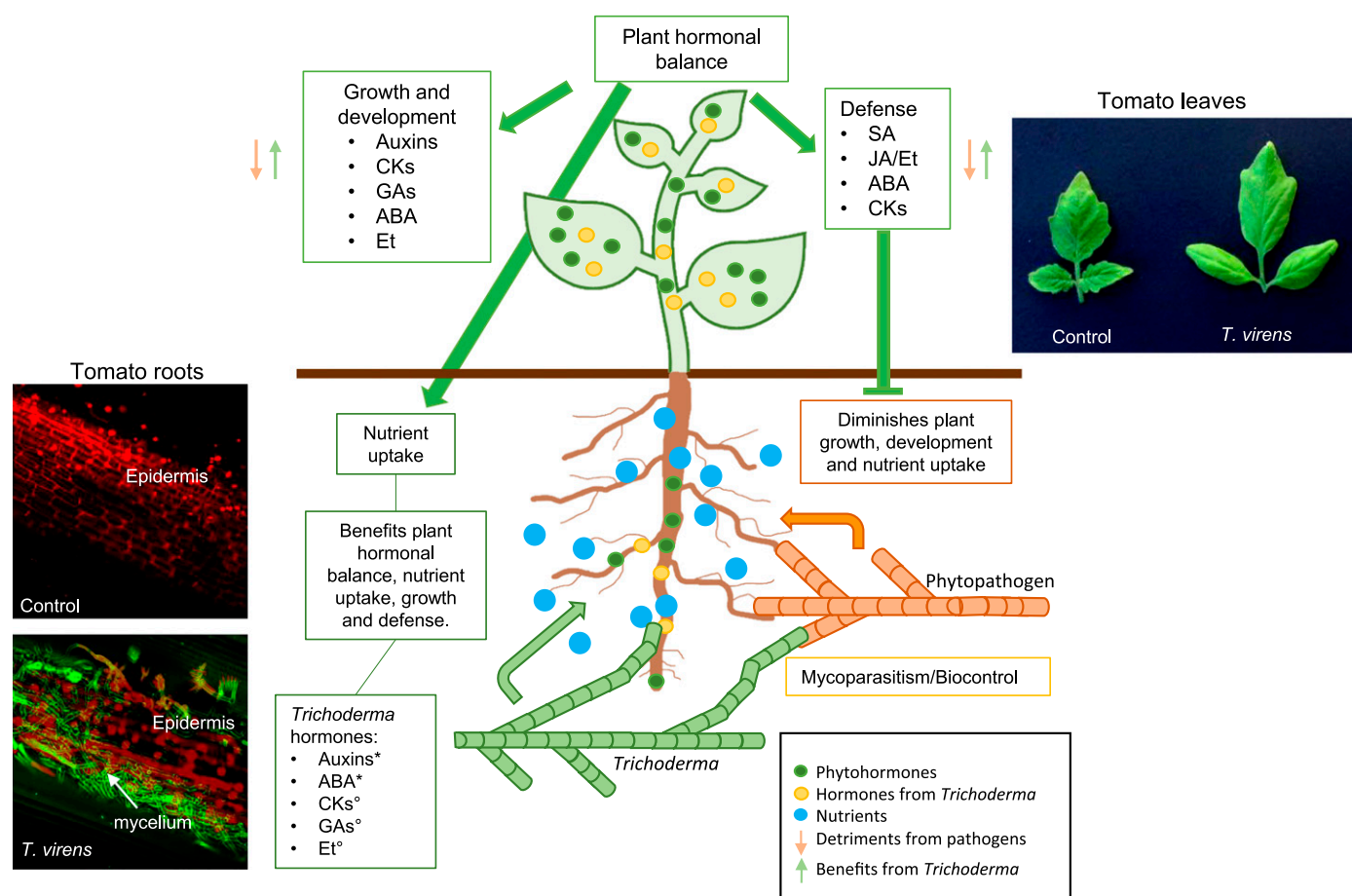


suggest that *Trichoderma* is capable of synthesizing these hormones, and that the production of CKs may be a characteristic shared with *C. purpurea*. There is evidence showing that various *T. harzianum* isolates reduce the total inactive CKs content in shoots of melon plants possibly due to the conversion of inactive to active CKs, which in conjunction with the effect of other phytohormones, such as IAA, ABA, and Et, the fungus uses to promote plant growth (Martínez-Medina et al. 2014). Given that we found genes that might be involved in CKs signaling, these compounds likely play a biological role in the fungus, such as hyphal branching, and may be involved in the *Trichoderma*–plant communication (Albrecht and Argueso 2017; Balmer et al. 2015; Shores et al. 2010).

**Gibberellins (GAs).** GAs are phytohormones that promote growth via the degradation of DELLA proteins, which repress growth (Sun 2011). They are known in fungi since their discovery in the 1920s in *Gibberella fujikuroi*, which causes foolish seedling disease and from which the name “gibberellins” is derived. GAS biological role in fungi is still not very clear, although these hormones are produced by several fungi, including *Neurospora crassa* (Chanclud and Morel 2016).

GAs biosynthesis in plants consists of a series of three steps: (i) biosynthesis of *ent*-kaurene from geranylgeranyldiphosphate (GGDP); (ii) conversion of *ent*-kaurene to GA<sub>12</sub> via cytochrome P450 monooxygenase; and (iii) synthesis of GA<sub>19</sub> and GA<sub>20</sub> in the cytoplasm.

Recently, the similarities and convergence in the GAs biosynthetic pathway between plants, fungi, and bacteria have been reviewed by Salazar-Cerezo et al. (2018). In contrast with plants, in fungi the genes responsible for GAs biosynthesis are found in clusters: one GGDP synthase gene (*ggs2*), the bifunctional *ent*-copalyl diphosphate synthase/*ent*-kaurene synthase (*cps/ks*), one desaturase (2-oxoglutarate-dependent dioxygenase, DES, that converts GA<sub>4</sub> to GA<sub>7</sub>) and three cytochrome P450 monooxygenases (P450-1, P450-2, and P450-3). Our bioinformatic survey of the *T. atroviride* genome allowed us to identify six genes, all related to GAs biosynthesis in *F. fujikuroi*, *Sphaceloma manihoticola*, *Metarhizium acridium*, or *Pseudomonas fluorescens*, with possible activities related to monooxygenases (IDs 293815 and 156885) geranylgeranyl pyrophosphate synthases (ID 160158), gibberellin oxidases (ID 302240), hydroxymethylglutaryl-CoA reductase (HmgR; ID 143946), and polyprenyl synthetases (ID 284926).



**FIGURE 2**

*Trichoderma* modifies plant hormonal balance. Plants cope with biotic and abiotic stresses by finely modulating a set of phytohormones that include auxins, cytokinins (CKs), gibberellins (GAs), abscisic acid (ABA), ethylene (Et), salicylic acid (SA), and jasmonic acid (JA) (green circles). This hormonal balance provides defense against pathogens, enables nutrient uptake (blue circles) from the soil, and allows proper growth and development of the plant (upper right image, tomato-control leaf). When faced with a pathogen (brown hyphae), the plant hormonal balance is compromised, and the result is a detriment to the overall plant health (brown arrows). *Trichoderma* has the potential to produce hormones (°), while there is evidence of the production of auxins and possibly ABA (\*). When *Trichoderma* is present in the rhizosphere (green hyphae), it protects the plant by attacking phytopathogens, as a mycoparasite. Thus, when *Trichoderma* interacts with the plant, colonizing its roots (bottom left images), there is a modification in the hormonal balance of the plant, mediated by *Trichoderma*-derived hormones (yellow circles), improving plant health and vigor (small green arrows, upper right image, tomato-*T. virens* leaf).

GAs are less studied in plant–microbe interactions, but their possible role may pose an interesting research subject. It is known that the degradation of DELLA proteins via GAs signaling releases the JA signaling repressor JAZ1, reducing JA-responsive gene expression (Hou et al. 2010), enhancing SA signaling and biotrophic resistance (Pieterse et al. 2012). According to Salazar–Cerezo and coworkers (2018), GAs as secondary metabolites are not essential for fungal growth or development, but because their production occurs mainly when the fungi are exposed to a hostile environment, these compounds may have been advantageous for survival in their ecological niche. In *F. fujikuroi*, the presence of GAs is associated with the capacity of the fungus to infect rice plants (Wiemann et al. 2013), and the expression of the *des* gene in *Solanum nigrum* and *S. dulcamara* plants resulted in increased plant growth accompanied by a higher concentration of GA<sub>3</sub> (Bhattacharya et al. 2012). Since we found in the *Trichoderma* genome 16 sequences related to DES activity, *Trichoderma* could promote plant growth by increasing the amount of GAs in the plant, in consequence augmenting plant biomass. There is also evidence that the endophytic fungus *Penicillium foniculosum* LHL06 secretes GA<sub>1</sub>, GA<sub>4</sub>, GA<sub>8</sub>, and GA<sub>9</sub> under copper stress conditions, and the application of its culture medium, rich in bioactive GAs, to soybean plants reduced abiotic stress produced by copper (Khan and Lee 2013).

Although most of the enzymes required for GAs biosynthesis are encoded in the *T. atroviride* genome, we didn't find sequences coding for one of the key enzymes of the GAs biosynthesis pathway: the *ent*-copalyl diphosphate synthase/*ent*-kaurene synthase (*cps/ks*) which catalyze the intermediate steps of GAs biosynthesis (Albermann et al. 2013). Thus, it is unlikely that *T. atroviride* can produce GAs.

**Ethylene.** Ethylene is a gaseous phytohormone with roles in seed germination, fruit ripening and plant senescence (Bleecker and Kende 2000). Et also plays a role in plant immunity, affecting both the SA and the JA pathways (Pieterse et al. 2012). In plants, Et biosynthesis begins with S-adenosyl-L-methionine (S-AdoMet) and 1-aminocyclopropane-1-carboxylic acid (ACC) as precursors, and the main enzymes catalyzing this pathway are as follow: (i) S-AdoMet synthetase (SAM), (ii) ACC synthase (ACS), and (iii) ACC oxidase (ACO) (Wang et al. 2002). *Penicillium digitatum*, *B. cinerea*, and *F. oxysporum* among other fungi are known to produce ethylene (Chanclud and Morel 2016; Tudzynski and Sharon 2002). In fungi, Et affects spore germination and hyphal growth. The biosynthetic pathway for Et is known in *B. cinerea*, which uses methionine as precursor of  $\alpha$ -keto  $\gamma$ -methylthiobutyric acid (KIMBA) to produce ethylene (Chague et al. 2002).

Our bioinformatic analyses indicated the presence of six genes in the *T. atroviride* genome that are related to Et biosynthesis in *B. cinerea*, *T. asperellum*, *P. patens*, or *Pseudomonas* sp. (Table 1). The genes putatively involved in Et biosynthesis encode an S-adenosylmethionine synthetase (ID 301763), a 1-aminocyclopropane-1-carboxylate synthase (ID 297477), and member of the Iron/ascorbate family of oxidoreductases (ID 39146), suggesting that this fungus could have a functional ACC synthase pathway leading to the production of Et (Wang et al. 2002).

Et not only directly affects the physiology of the plant, but it is also related to nutrient stress. When the plant is subjected to nutrient limitation, there is an increase in the amount of ethylene, which results in enhanced auxin sensitivity and ethylene perception, leading to stress tolerance (Iqbal et al. 2013). One of the benefits of the interaction with *Trichoderma* for the plant is enhanced biotic and abiotic stress resistance (Mukherjee et al. 2013). The presence of genes related to Et biosynthesis in the genome of *T. atroviride* suggests that the production of this molecule by the fungus may be implicated in the plant tolerance to several types of stress.

**Abscisic acid (ABA).** ABA is a phytohormone that controls seed dormancy and development, stomatal aperture and promotes tolerance to abiotic stresses like drought and high salinity in plants (Hauser et al. 2011). In plant–pathogen interactions, ABA affects

defense in a positive or negative manner, as reviewed by Asselbergh et al. (2008). ABA has a positive effect in the interaction between *A. thaliana* and *P. syringae*, or a negative one when interacting with *Alternaria brassicicola*, for example (Asselbergh et al. 2008). ABA can also affect SA–JA cross talk, regulating basal defenses, although, according to Flors et al. (2008), the molecular details are still poorly understood.

There is evidence of production of ABA by several fungi (Tudzynski and Sharon 2002; Chanclud and Morel 2016). The main role proposed for this fungal phytohormone is as a virulence factor promoting plant infection, as it has been shown to be involved in the *M. oryzae*–rice interaction (Jiang et al. 2010); and that accumulates at the early stages of the *U. maydis*–maize interaction (Morrison et al. 2015).

In *B. cinerea*, the biosynthetic pathway from isopentenyl diphosphate has been reported (Inomata et al. 2004), involving the genes *bcaba1*, *bcaba2*, *bcaba3*, and *bcaba4* (Gong et al. 2014), homologs to the *Arabidopsis ataba1*, *ataba2*, *ataba3*, and *ataba4* genes that catalyze the final steps of ABA biosynthesis (Dong et al. 2015). We identified six genes related to the ABA biosynthesis pathway (Table 1) of *Arabidopsis*, *B. cinerea* or *Agrobacterium tumefaciens* in the genome of *T. atroviride*, with putative xanthine oxidase/aldehyde oxidase (ID 141294) and short-chain-dehydrogenase/reductase (ID 158420) functions, and homologs to the *B. cinerea bcaba1*, *bcaba2* and *bcaba4* genes (IDs 80521, 295125, and 28537, respectively), providing an almost complete ABA biosynthesis pathway. We did not find a homolog of *bcaba3/ataba3* in the *T. atroviride* genome. The enzyme encoded by this gene is key for the final step of ABA biosynthesis in *A. thaliana*, providing the necessary molybdenum cofactor to the AAO3 enzyme, which converts abscisic aldehyde to ABA (Dong et al. 2015). Without this gene, there is no production of active ABA. Our findings suggest that *T. atroviride* may not produce the active hormone but may be capable of producing the immediate precursor: abscisic aldehyde, which could be delivered into the plant during the interaction, where it could be transformed into ABA by the plant respective enzymes.

There is evidence suggesting that *T. virens* and *T. atroviride* are capable of modulating ABA in plants. Contreras-Cornejo et al. (2015) found that strains of both species are capable of modulating leaf transpiration and stomatal aperture in *A. thaliana* by inducing an ABA receptor. Thus, *Trichoderma*-derived ABA precursor could participate in regulating stomatal aperture in *Arabidopsis*, enhancing water stress tolerance in the plant. This would represent yet another mechanism through which *Trichoderma* could help counteract the effects of environmental stress on plants (Fig. 2).

## CONCLUSIONS

The search for alternatives to chemical fertilizers and pesticides, in order to improve soil fertility and crop yield, led us to take a closer look at the interactions that take place in the rhizosphere. The global study of the microorganisms associated with plants, the plant microbiome, is gaining interest and has the potential to identify ways to obtain healthier crops and reduce or replace the use of agrochemicals. The diversity of the plant microbiome can greatly influence the general outcome of the plant growth and development (Etalo et al. 2018).

Fungi from the genus *Trichoderma* are well-known plant symbionts that exert a positive effect on plant growth, development, crop yield, and elicitation of plant defense responses through the modulation of plant hormonal mechanisms and production of several secondary metabolites (Hermosa et al. 2012; Van der Ent et al. 2009). In addition, these fungi are effective mycoparasites (Fig. 1) against plant pathogens and protect plants against them (Benítez et al. 2004). These characteristics make *Trichoderma* an excellent subject for exploration for its positive potential as an important part of the healthy plant holobiont.



In recent years, manipulation of the plant microbiome has been proposed as a biocontrol strategy in the field. According to Berg et al. (2017), the use of organisms capable of modifying the plant microbiome structure and interactions will lead to the development of new “microbiome-based biocontrol strategies,” helping the plants defend themselves against pathogens. The composition of the plant microbiome can lead to two important outcomes in agricultural fields: *plant health*, when the microbiome is diverse and there is a metabolic cooperation, nutrient and hormonal exchange between the plant host and microbiome; or *plant disease*, when the microbiome interacts with pathogens in a synergistic way, affecting overall plant health (Berg et al. 2017). The diversity of the microbiome is crucial to plant health and it can switch very easily from promoting plant health to promoting plant disease (Yan et al. 2017). In plant health, the organisms that are part of the microbiome influence nutrient and hormonal balance, leading to an increase in plant production. Plant-beneficial microbes like mycorrhizal fungi, nodule-forming bacteria, and plant endophytes are among the most influential organisms in the plant microbiome structure (Berg et al. 2017).

The mechanisms exerted by *Trichoderma* on the plant are diverse, from preventing phytopathogens from attacking the plant, to enhancing plant health and defenses. Recent studies raised the possibility that not only are effectors and secondary metabolites involved in the fungus–plant interaction, but fungal-derived hormones may have a role as well. One of the least explored mechanisms in the *Trichoderma*–plant interaction is the effect of fungal-derived hormones. *Trichoderma* produces auxins and an ABA precursor, and it may also produce CKs and Et that together may add to the plethora of ways in which this fungus interacts with its plant host, explaining many of the benefits reported as result of the *Trichoderma*–plant interaction.

The impact of the presence in the rhizosphere of *Trichoderma* on plants is summarized and represented in Figure 2, which highlights root colonization, leading to the increase in plant growth, protection against phytopathogens by mycoparasitism, and preparation against biotic and abiotic stressors through the participation of secondary metabolites, effectors, and the modulation of the hormonal balance.

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