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Mechanisms Involved in Nematode Control by Endophytic Fungi

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Abstract

Colonization of plants by particular endophytic fungi can provide plants with improved defenses toward nematodes. Evidently, such endophytes can be important in developing more sustainable agricultural practices. The mechanisms playing a role in this quantitative antagonism are poorly understood but most likely multifactorial. This knowledge gap obstructs the progress regarding the development of endophytes or endophyte-derived constituents into biocontrol agents. In part, this may be caused by the fact that endophytic fungi form a rather heterogeneous group. By combining the knowledge of the currently characterized antagonistic endophytic fungi and their effects on nematode behavior and biology with the knowledge of microbial competition and induced plant defenses, the various mechanisms by which this nematode antagonism operates or may operate are discussed. Now that new technologies are becoming available and more accessible, the currently unresolved mechanisms can be studied in greater detail than ever before.

INTRODUCTION

Since the first discoveries made by Miles Joseph Berkeley and Heinrich Anton de Bary in the mid-nineteenth century, the influences of microorganisms on plants have been studied with growing intensity. Not without reason, the focus has primarily laid on those microorganisms that are pathogenic and cause plant diseases, which sometimes lead to devastating crop losses, such as late blight in potato, Panama disease in banana, rusts in cereals, and brown spot in rice (75, 94). With the exception of the arbuscular mycorrhizae (AMs) and rhizobia (32), plant-associated microorganisms that establish mutual beneficial or other more cryptic interactions have been little studied. This is, however, changing rapidly, as it is now evident that plants have intricate relationships with an array of microorganisms, particularly bacteria and fungi, that can lead to an increase in plant vigor, growth, and development as well as changes in plant metabolism (2, 11, 88, 138). Such beneficial microorganisms may thus be very valuable for the development of more productive and sustainable agricultural practices or for the production of chemicals for pharmacological purposes (2, 11, 88, 138). A classic example of demonstrating that the presence of a particular microorganism can be an asset in modern agriculture is the managing of take-all disease through monoculture of wheat (27, 156). Take-all is one of the global major root diseases in wheat and is caused by the soilborne fungus *Gaeumannomyces graminis* var. *tritici*. Because of the lack of resistant varieties, the disease is controlled by crop rotation, tillage, and, with limited success, chemicals in order to reduce the fungal inoculum for the following years. Remarkably, as initially observed in the large wheat-growing areas of the Inland Pacific Northwest of the United States, a wheat monoculture can also dramatically reduce the occurrence of the disease. This positive effect of a rather counterintuitive growth strategy is associated with a shift in the soil microbial community due to the continuous presence of wheat, leading to the accumulation of antibiotic-producing pseudomonads, which are antagonistic toward the wheat pathogen. In the wheat monoculture, the take-all disease may be severe in the first years but then spontaneously declines to relatively stable levels that are hardly damaging for decades, hence the description of this phenomenon as take-all decline (27, 156). Thus, when continuously cultivated, wheat can cure itself of a disease by facilitating the proliferation of particular antagonistic microorganisms in the soil.

In several other instances, it has been shown that particular soil microorganisms, especially those found in the rhizosphere, can lead to belowground and aboveground control of pests and diseases (11, 157). However, the microbial community structures of soil and, specifically, rhizosphere environments are extremely variable in place and time. This variability is most likely regulated by abiotic factors, such as soil type and geographical location, and biotic factors, such as the variations in components released by the root of the various plant species and that consist of root cap, border and other cells, insoluble mucilage, and soluble exudates as well as volatile organic carbons (10, 61, 74, 154). Metagenomic studies have shown that not only the plant species but also the plant genotype (100, 101, 155) and growth stage (71) can affect the community structure of the rhizosphere. Nevertheless, the soil microbiome contains a vast number of species, and managing those in a cropping system to acquire protection against pathogens can be difficult. Inundation of the soil by antagonistic microorganisms (39) would require a significant amount of inoculum and, even when feasible, may not lead to the anticipated result, simply because the introduced microorganism cannot compete with the already present complex natural microbial population and thus cannot further proliferate (71).

The microbial community within the root endosphere is significantly less complex (24, 38, 150) and, as a consequence, may be more easy to modulate, e.g., by preinoculation of planting material with beneficial root colonizers, thus allowing beneficial microbes to competitively

establish themselves inside the host plant before other microbes can (139). It is now evident that, in nature, virtually every plant species is colonized by microorganisms, which in many cases do not elicit visible disease symptoms (120). In fact, this apparent lack of provoking a visible phenotype is also the reason why the presence of such endophytes has often been overlooked in the first place. Like their rhizosphere-associated relatives, plant-colonizing microbes (termed endophytes) can be beneficial for plants, leading to mutualistic or synergistic interactions (92). The plant is considered to serve as a protective environment and an important carbon source for the microbe, whereas the benefit for the plant is often more difficult to define. Similar to AMs and rhizobia, the plant can benefit through an increased nutrient uptake (49). In other cases, the benefits for the host plant may be more indirect and complex, which can be determined only by looking at the environmental or ecological framework (104, 129). Similar to AMs and rhizobia (18, 32), endophytes can increase both tolerance and resistance to various biotic and abiotic stress situations (4, 104, 126, 134). For example, in grasses, specific endophytes are considered major factors in the overall host fitness and the protection against herbivory (104, 165).

Because of environmental and human health concerns, the use of pesticides is being restricted in pest and disease management practices in agriculture. The application of endophytes for the control of pests and diseases may therefore be a valuable alternative. As they are, in many cases, facultative biotrophs, endophytes can, contrary to the obligate biotrophic AMs, be relatively easily produced and employed through various methods to all kinds of crops.

This review focuses on the current knowledge of endophytes that display antagonistic activity in planta toward plant-parasitic and entomopathogenic nematodes. Although still fragmented, the accumulated biological and molecular data provide valuable insights into the various mechanisms by which this antagonism operates or may operate.

PLANT-PARASITIC AND ENTOMOPATHOGENIC NEMATODES

Plant-parasitic nematodes are essentially biotrophic parasites with, depending on the genus, different lifestyles: They can be migratory, foraging on living plant cells and killing those in the process, or they can be sedentary, establishing a sophisticated and strictly long-term interaction with particular root cells that are converted into nurse cells (50, 53). Both lifestyles can dramatically affect plant growth and development, a problem that can affect agricultural production at a global level. The genus *Meloidogyne* contains exclusively sedentary species, collectively called root-knot nematodes (RKNs), with a sometimes extremely wide host range, such as *Meloidogyne incognita* and *Meloidogyne arenaria*, affecting almost every important crop in the world, e.g., rice, potato, tomato, soybean, peanut, sweet potato, cassava, and cotton (87, 147). Migratory nematodes, such as the burrowing nematode *Radopholus similis*, the causal agent of the toppling disease in banana cultures, and *Bursaphelenchus* species, which rapidly kill coconut and pine trees on a massive scale, can wreak havoc as well (48, 87). Both migratory and sedentary nematodes are extremely difficult to control in agriculture. Particularly, the use of chemicals is not always effective and can even be hazardous from the perspective of environmental safety and human health. Resistant crop plant varieties are rarely available and have their limitations, and crop rotation is not always feasible because of economic considerations or the wide host range of some nematode species (16). Additional nematode control strategies through the application of endophytes could support the development of more sustainable agricultural practices (168). Entomopathogenic nematodes are parasites of insects and therefore operate at a higher trophic level when compared with plant-parasitic nematodes. They are, in fact, bacterial feeding nematodes and by means of the specific bacteria they carry and release inside the larvae, the insects are killed. The bacterium, which consumes the insect, serves then as

a food source for the nematode. Applying entomopathogenic nematodes as a biocontrol agent can be an effective approach to contain soilborne herbivorous insects (86).

MICROBIAL ENDOPHYTES

Microbial endophytes form a heterogeneous group, primarily consisting of bacteria and fungi. The definition of an endophyte is far from robust and is rather controversial. Essentially, it refers to an organism that colonizes a plant at a certain point during its life, irrespective of having a beneficial, detrimental, or neutral impact on the host plant when doing so. But over the years the definition has evolved, indicating not only the location where this organism resides (i.e., inside the plant) but also the type of association with the plant, which is characterized as being neutral or beneficial (111, 143, 159). In this way, the term endophyte becomes more meaningful and serves as an opposite to the term pathogen. However, defining an endophyte in this way is by no means solid, because microorganisms can be very dynamic in their behavior and for several endophytes, depending on the physiological and developmental stage of both plant and endophyte, disease symptoms can be elicited (77, 132, 159). For this, the outcome of the association between microorganisms and plants can be described as a continuum in which pathogens can be found at one end and true endophytes (103, 159) at the other end (132, 159). True endophytes have mastered the association with their host plant to the point that they never provoke any visual symptoms during colonization of and subsequent proliferation inside the plant. This continuous balanced association is often mutualistic (19, 132). Given that they can be so elusive, the presence of true endophytes inside plants is often overlooked. Because of the formation of arbuscules, which are specialized fungal structures responsible for nutrient transfer between fungus and roots, and their proliferation into the rhizosphere, AMs are set aside from endophytic fungi (19, 122, 159).

ENDOPHYTIC FUNGI

The endophytic fungi are categorized on the basis of their ecology into the balanciaceous endophytes and the nonbalanciaceous endophytes (132). The balanciaceous endophytes, also referred to as grass endophytes, are phylogenetically related and comprise the genera *Epicloë* and *Balansia* (anamorphs *Neotyphodium* and *Ephelis*, respectively) within the ascomycetes (132). These obligate symbionts are transmitted both vertically and horizontally, grow intercellularly in a strictly controlled fashion in the aboveground plant tissue, and produce specific structures facilitating the uptake of nutrients into their mycelium. Depending on the species, some grass endophytes manifest themselves at a certain point as being antagonistic to their host, suppressing seed production (choke disease), thus preventing vertical transmission, whereas others are much more elusive and mutualistic, supporting growth and development and increasing desiccation tolerance of the host (129). By the in planta production of an array of alkaloids, which are toxic to not only insects and nematodes but also, unfortunately, to vertebrates, the host is protected against herbivory (6, 128). The nonbalanciaceous endophytes can be found within a range of genera of the ascomycetes, such as *Alternaria*, *Colletotrichum*, *Fusarium*, *Trichoderma*, and *Acremonium*, and, to a lesser extent, basidiomycetes, with *Piriformospora indica* as the best-known example (115). The genus *Fusarium* is particularly over-represented when plant roots are analyzed for the presence of endophytes, with *Fusarium oxysporum* being the most prominent and cosmopolitan species (9, 77, 91). And, although all are saprophytically competent and particularly known for the various pathogenic isolates, which are subsequently grouped in formae speciales on the basis of their host plant species, the majority of the *F. oxysporum* isolates are harmless and can even be beneficial endophytes by antagonizing fungal pathogens, plant-parasitic nematodes, and insects (1, 54, 56). This and the presence of a continuum between them emphasize that plant pathogens and endophytes may in fact be quite

similar. Consequently, the nature of an invading microorganism can primarily be established at the isolate level rather than species level and is also determined by the host plant the invader colonizes and the developmental stage of the invader. *P. indica*, initially isolated from the rhizosphere of shrubs found in the Thar Desert of Rajasthan, India (151), shows all the characteristics of an endophyte by promoting plant growth and supporting the plant in resisting biotic and abiotic stress elements. Still, this fungus has a rather aggressive lifestyle when colonizing and proliferating. It induces cell death inside the roots; however, this does not occur within the vascular tissue, thus the development and functioning of the root are not harmed (33, 72, 115). Phenotypically, an endophytic isolate of *Fusarium verticillioides* systemically proliferated intercellularly, whereas a pathogenic strain also colonized intracellularly (8). A phylogenetic analysis, based on sequences of the ribosomal intergenic spacers (IGSs), revealed that not all endophytic *F. oxysporum*, capable of colonizing banana, could be distinguished from pathogenic *F. oxysporum* f. sp. *cubense* isolates (80). *Colletotrichum* species, pathogenic on particular hosts, were found to behave as endophytes in other plant species. Some of those could even support previously unknown hosts with respect to growth, disease resistance, and drought tolerance (116). Through a single allelic mutation, a pathogen can turn into a microorganism displaying a completely endophytic lifestyle, as was demonstrated for *Colletotrichum magna* in susceptible watermelon cultivars (44). In addition, the presence of this path-1 mutant prevented the wild type and an unrelated pathogen, *F. oxysporum* f. sp. *niveum*, from eliciting disease in watermelon, although both pathogens were able to infect the host. Conversely, disruption of the stress-activated mitogen-activated protein kinase *sakA* in the grass endophyte *Epichloë festucae* resulted in a mutant that proliferated more vigorously inside the host and provoked disease responses, such as premature senescence and disruption of the normal plant phenotype and growth (37). At the molecular level, the infected host plants also responded differently to the *sakA* mutant, accumulating transcripts that are typical for defense against pathogens.

FINDING ENDOPHYTIC FUNGI ANTAGONISTIC TOWARD NEMATODES

Until now, the screening for and characterization of beneficial endophytic fungi against plant-parasitic nematodes are generally highly biased toward fungi that can easily be cultured in vitro and may be suitable for mass production. Surface-sterilized roots of the plant of interest are placed on growth media suitable for fungal growth. Sometimes an antibiotic is added to prevent endophytic bacteria from proliferating. Fungi that emerge from the roots are transferred to fresh media to verify their growth on artificial media and their ability to sporulate. When sporulating, an endophyte is more suitable in production systems for biocontrol agents. An appropriate endophyte is subsequently reintroduced into a host plant, which is not necessarily the plant it was isolated from. After inoculating the nematode, nematode colonization is compared with an endophyte-free plant. When sedentary RKNs are used, the severity of root galling is in many cases compared in this initial screen to simplify this rather labor-intensive step. Based on the results, a subset of potential interesting antagonistic endophytes is selected and their effects on nematodes are further evaluated.

The chances of encountering a nematode antagonist in such an initial screening system seem substantial. Of the fungal endophytes isolated from tomato roots, approximately 60% had a neutral effect, 20% had a stimulating effect, and 20% had a negative effect on *M. incognita* after reinoculation of tomato (139). In another rather elaborate study, cucumber plants were cultivated in 87 different soils samples gathered from tropical, subtropical, and temperate climatic regions (162). Subsequently, a total of 514 endophytic fungi were collected from roots, stems, and leaves of 7- to 10-day-old seedlings. Of the 294 endophytic fungi that could be cultivated on PDA and

could sporulate, 23 isolates (approximately 8%) significantly reduced the number of galls formed upon *M. incognita* infection in a greenhouse trial. Of the ten best performing isolates, nematode control efficacies varied from 16% to 44%. Of the 16 encountered genera, isolates from *Fusarium*, *Trichoderma*, *Chaetomium*, *Paecilomyces*, *Phyllosticta*, and *Acremonium* were best performing. This illustrates that although they may have a negative impact on the nematode, there can still be a significant range in the antagonistic competence of each individual endophyte, even among the different isolates within one species. Similar observations were made for various endophytic *Trichoderma* and *Fusarium* isolates obtained from rice and tested against *Meloidogyne graminicola* (83) and endophytic *Fusarium* isolates obtained from banana and tested against *R. similis* (113). The reason for this variability in antagonism, even among isolates within the same species, is currently unknown. It may be associated with the level of root colonization or the level of induced plant defense responses by the particular plant species or cultivar (105, 106). The encountered genera among the most effective endophytes are nevertheless fairly typical, as over the years antagonistic endophytic isolates within *Fusarium*, *Trichoderma*, and *Paecilomyces* were frequently reported (57, 83, 105, 113, 125, 167). Additionally, endophytic isolates were found of the nematophagous nematodes *Arthrobotrys oligospora*, also known for its nematode trapping hyphae when growing in soil, *Acremonium implicatum*, and *Pochonia chlamydosporia* (syn. *Verticillium chlamydosporium*) (17, 93, 145). The grass endophyte *Neotyphodium coenophialum* can provide protection against not only aboveground herbivores but also sedentary and migratory nematodes, such as *M. incognita*, *Meloidogyne marylandi*, and *Pratylenchus scribneri* (40, 59, 73, 146, 158).

MECHANISMS EMPLOYED BY ENDOPHYTIC FUNGI THAT ARE ANTAGONISTIC TO NEMATODES

It is generally assumed that microorganisms benefit from the ability to colonize plants: They are protected against soil-bound competitors and have a direct access to carbon resources provided by the plant. An endophyte has therefore good reasons to compete with and protect its niche from other root-invading organisms, whether they are nematodes, bacteria, or fungi. The RKN *M. incognita* showed a preference for exudates extracted from tomato roots over those extracted from tomato roots colonized by the endophytic *F. oxysporum* strain Fo162 (**Figure 1**) (29). Such a preference was also observed for *M. graminicola* with respect to rice in the absence and presence of *Fusarium moniliforme* strain Fe14 (84). This indicates that the presence of the endophyte can make a host less attractive or more repulsive to a parasitic nematode.

Finding and entering the host plant are, however, not the only phases that can be affected by an antagonistic endophyte; postpenetration effects can also be observed. As mentioned above, sedentary plant-parasitic nematodes actively establish a sophisticated interaction with their host by converting particular root cells into syncytia (cyst nematodes) or giant cells (RKNs) and maintaining those for the duration of their development and reproduction. The nematode actively extracts its nourishment from only these feeding cells by means of its stylet (50, 53). In tomato, Fo162 attenuated or delayed the development of the *M. incognita* larvae into adult females and reduced fecundity (96). An attenuated or delayed development was also observed, together with an increase in the male-female ratio, for *M. graminicola* after inoculating rice with the endophytic Fe14 (84). With the notion that sex determination among RKNs is primarily epigenetically driven (21, 109), these postinfection effects collectively indicate that endophytes can negatively affect the induction of the giant cell to the point that the nematode has fundamental difficulties in extracting the required nourishment levels to perform optimally.

Overall, there is in many cases still much speculation on the specific mechanisms involved by which endophytes antagonize nematodes, but they are most likely diverse. Endophytes can directly

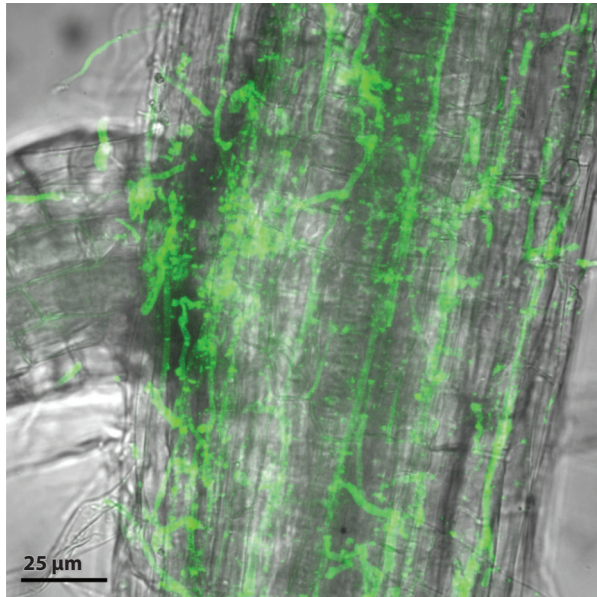


Figure 1

Confocal laser-scanning microcopy image of *Arabidopsis thaliana* colonized by the endophytic fungus *Fusarium oxysporum* strain Fo162. An inoculated root section was incubated in wheat germ agglutinin, which has an affinity for the chitin present in the fungal cell wall, conjugated with the fluorescent dye Alexa Fluor 488 (WGA-AF488, Molecular Probes). Fo162 has grown over the root surface and migrated intercellularly into the root cortex.

attack, kill, immobilize, or repel nematodes, confuse them when finding their host, interfere with nurse cell development, compete for resources, trigger plant defense responses, increase tolerance, or employ a combination of those options. The knowledge and ideas regarding these mechanisms are discussed in more detail below.

Attacking and Trapping

Nematophagous endophytic fungal isolates, such as isolates from *A. implicatum*, *Paecilomyces lilacinus*, *A. oligospora*, and *Trichoderma asperellum*, can trap or attack, kill, and devour nematodes either in the soil or in the roots (17, 42, 125, 141). Mechanical forces in the form of appressorial structures and lytic enzymes are used to enter nematode eggs, larvae, and adults (28, 85, 163). In vitro experiments have shown that *A. implicatum* can produce chitinases that play a role in penetrating nematode eggs. For the trapping fungus *A. oligospora*, the endophytic strains of this species perform better in controlling nematodes than the soilborne strains. It has been suggested that the endophytic strains can sustain themselves better compared with soilborne isolates. The host plant thus supports the endophyte when it is proliferating into the rhizosphere and producing their trapping structures (17).

Competition for Resources

The delayed nematode development and reduced fecundity (84, 96) may be attributed to a direct competition for sugars from the giant cells by the endophyte. Because there is an intense transport of sugars from phloem into the giant cell (66, 67), this could be an important target for

endophytes to obtain their nutrients (96). Recently, a new class of plant sugar transporters (SWEET) was identified that plays a role in the loading of sugars from the phloem parenchyma, via the apoplast, into the phloem companion cell (22, 23). Because bacterial symbionts and fungal and bacterial pathogens were capable of inducing SWEET gene expression, it is assumed that these microorganisms force the sugar translocation into the apoplast, thus facilitating direct access to sugars for their own benefit (22). Verifying SWEET gene expression in the roots as a whole, and in the giant cells in particular, in the presence and absence of an endophyte could therefore shed light on the access of endophytes to sugars.

Endophytic Nematostatic or Nematocidal Metabolites

Fungal endophytes, like most fungi, have the ability to produce an array of secondary metabolites for which the activity and the biological role can sometimes only be guessed (2, 144, 166). Some of those produced by endophytes may affect the nematode, e.g., by killing, paralyzing, repelling, or confusing them during the finding of their host plant. The balanciaceous endophytes are known for their antagonistic activity toward herbivores due to the various toxic metabolites they synthesize. Some, but not all, grass-*Neotyphodium* associations also lead to resistance to sedentary and migratory plant-parasitic nematodes (59). Undiluted culture filtrates of several *Neotyphodium* species caused mortality among preparasitic *M. incognita* larvae (73). When those culture filtrates were administered to the soil, fewer larvae infected cucumber roots. The antagonistic activity is attributed to the types of mycotoxins synthesized, which, because the endophyte resides in the upper plant parts, are basipetally transported into the root system. Loline, ergovaline, and α -ergocryptine have nematocidal activity, whereas ergocornine and ergonovine are generally nematostatic (6, 7). Ergovaline had a repelling effect on the nematode at both high and low concentrations, and N-formyllooline was an attractant at concentrations lower than 20 $\mu\text{g/ml}$, although it served as a repellent at higher concentrations (6). However, disruption of the ergot alkaloid biosynthesis did not alter the negative effect of the ryegrass-endophyte association with *P. scribneri*. In addition, the ergot alkaloid accumulation in the pseudostem was undetectable or not high enough to explain the resistance to the nematode, although this was measured in the absence of nematode infection (108). Other work shows that loline accumulation could nevertheless reach nematocidal levels inside roots, suggesting that, together with other factors, this mycotoxin does play a role in the defense against nematodes (7, 20).

Remarkably, there are indications that nematodes operating at a higher trophic level can also be affected by toxins produced by grass endophytes. When feeding on ryegrass, *Lolium perenne*, infected with *Neotyphodium lolii*, a reduction in mortality of the fall armyworm *Spodoptera frugiperda* due to the infection with the entomopathogenic nematode *Steinernema carpocapsae* was observed (119). *S. carpocapsae* was also less mortal to fourth and fifth instars of the black cutworm *Agrotis ipsilon* when feeding on *N. lolii* infected ryegrass (78). Of the various ergot alkaloids that can be produced by *N. lolii*, ergonovine malate increased and ergocristine decreased the rates of nematode infection toward black cutworm. In vitro experiments demonstrated an inhibited growth of *Xenorhabdus nematophila*, the symbiotic bacterium of *S. carpocapsae*, in the presence of ergocristine (79). Even though the larvae had a significantly lower biomass when growing on endophyte-infected ryegrass, it is assumed that the herbivore has adapted to the ergot alkaloids and, at the same time, exploited these alkaloids to its own advantage against the entomopathogenic nematode's symbiotic bacterium, which is essential for parasitism (119).

The nonbalanciaceous endophytes, including the *Fusarium*, *Acremonium*, *Trichoderma*, *Chaetomium*, and *Paecilomyces* species, can all produce numerous metabolites under in vitro conditions. When *Acremonium strictum*, *A. implicatum*, *P. lilacinus*, and *Trichoderma harzianum* were

grown in liquid media, their culture filtrates were toxic to *M. incognita* second-stage preparasitic juveniles (52, 145). For Fo162, the culture filtrates contained components that significantly affected several of the tested nematodes species but not all (3, 5, 58). Preparasitic juveniles of *Heterodera schachtii*, *M. incognita*, *Meloidogyne javanica*, and *M. arenaria* were fully inactivated. However, inactivation occurred for only 60% of mixed stages of the migratory endoparasites *R. similis* and *Pratylenchus zaei* and did not occur at all for the mycophagous species *Aphelenchoides composticola* and microphagous species *Panagrellus redivivus*. It is suggested that the larval stages were more sensitive to these culture filtrates (59). Both exudates and cell wall extracts, obtained from the endophytic basidiomycete *P. indica*, affected vigor, infectivity, development, and fecundity of the sedentary cyst nematode *H. schachtii* (30).

It remains to be determined how relevant these findings are, as the toxic components have not yet been characterized, nor has the level of their accumulation in plant roots. The artificial growth medium and culture do not really reflect natural conditions, and alternative fermentation methods that better resemble conditions encountered by the endophytes in their host plants, such as growth on semidry plant solids, may lead to the synthesis of other more relevant compounds (C. Bogner, A. Schouten, P. Proksch, unpublished results). Moreover, by combining the biosynthesis pathways of endophyte and plant, additional compounds can be synthesized that cannot be synthesized by the endophyte alone (88). The endophyte can initiate or stimulate particular biosynthesis pathways in the plant host, provide parallel biosynthetic pathways, and further derivatize or metabolize host-derived compounds. Conversely, the host plant can initiate or stimulate particular biosynthesis pathways in the endophyte and further derivatize or metabolize endophyte-derived compounds (88). When inoculated with Fo162, changes in the accumulation of organic compounds in tomato leaves were reported (99). So far, the nature and activity of these compounds have not been resolved.

Endophytes Producing Plant Hormones

Like many bacteria and fungi, endophytic fungi can produce plant hormones, such as auxins, cytokinins, and gibberellins, *in vitro* (2, 117, 144, 166). The typical auxin-related phenotypes, e.g., increased biomass or accelerated root development, were observed after *Arabidopsis* seedlings were inoculated with either *Trichoderma virens* or *Trichoderma atroviride*. Mutant analysis showed that disruption of auxin transport or signaling reduced growth promotion and increased root proliferation after *T. virens* inoculation (26). *In vitro* experiments with *Arabidopsis* showed an increase in root and root proliferation in the presence of Fo162 (97), and recently indole acetic acid (IAA) was detected in *in vitro* cultures of this endophyte (C. Bogner, A. Schouten, P. Proksch, unpublished results). An endophytic strain of the nematophagous *P. chlamydosporia* was reported to produce IAA in *in vitro* cultures. An increase in root growth may increase nematode infection tolerance because it compensates for the restricted water transport (62, 63, 70).

The *in planta* synthesis of hormones or functional analogs by endophytes may also have a more direct impact on the infecting nematode. Sedentary plant-parasitic nematodes carefully manipulate pathways responsive to auxins, ethylene, and, possibly, other phytohormones, which are crucial to establish and maintain the nurse cells (50). *H. schachtii* and *M. incognita* could both produce exudates containing various cytokinins, with benzyladenine and zeatin-type cytokinins being the most dominant forms, at high enough concentrations to affect the physiological processes inside a host plant (31). Recently, it was reported that the silencing of a cytokinin-synthesizing isopentenyltransferase gene in *H. schachtii* led to a reduction in nurse cell expansion (136). The endophyte *P. indica* was shown to produce cytokinins and infection with *P. indica* resulted in higher *in planta* cytokinin levels. And by testing various mutants, such as those lacking *cis*-zeatin or containing

reduced cytokinin levels, it was suggested that cytokinins are mandatory for *P. indica*-induced growth promotion (148). This would suggest that endophytes could even support a proper establishment of sedentary plant-parasitic nematodes. However, a too-high cytokinin level may still have negative side effects, such as the disruption of the normally tightly coordinated balance with auxins (102) or the increase of plant defenses by the accumulation of particular phytoalexins (55).

Mobilizing Plant Defenses

Although endophytes may colonize their host without causing apparent disease symptoms, it is now generally accepted that plants respond to their presence (122), often in a systemic way. To biologically determine systemic effects of root-associated endophytes on nematodes, a split-root assay is commonly used in which the root system of a plant is physically separated into two and the inducing agent is introduced into one half (inducer side) while the affected organism is introduced into the other half (responder side) (149). In this way, it was demonstrated that Fo162 antagonized the colonization of *R. similis* in banana and *M. incognita* in tomato and *Arabidopsis* (29, 97, 153). In rice, systemic induced resistance was also observed for Fe14 against *M. graminicola* (84). Similar observations were made for banana in a more complex combined twin-pot split-root assay, in which the inducer side contained either *F. oxysporum* strain Fo162 or V5W2 and the responder side was connected to the root system of a noninoculated plant by a tube. *R. similis* released in the connecting tube had a preference for the roots of the noninoculated plant (140), emphasizing that the repellency or lack of attraction was systemic.

The initial plant responses to endophytes may be similar to immune responses detected in the interaction with pathogenic microorganisms, which is subsequently modulated during later stages of the interaction, thus enabling a successful colonization of the host plant while simultaneously priming the plant for defense against other microorganisms (164). Priming describes a latent form of induced resistance, also at the molecular level, as there is no apparent accumulation of defense-related transcripts, such as those coding for phenyl ammonia lyase (PAL) and pathogenesis-related (PR) proteins. However, upon additional biotic or abiotic stresses, such as root-associated microorganisms, particular synthetic compounds, pathogens, and herbivores, defense responses are activated and can be observed at the molecular level by an often dramatic increase of the defense-related transcripts (25, 46, 64, 112).

The endophytic nematophagous *A. oligospora* and *P. chlamydosporia* induced the formation of papillae and other cell wall appositions in barley and tomato, respectively (42, 82). These cell wall structures are associated with plant resistance but can be elicited by both pathogenic and non-pathogenic fungi (14, 15, 65). Although at different levels, both endophytes were nevertheless able to proliferate inside the roots. Given that the plant does respond to the endophyte by the deposition of phenolics (including lignin), proteins, and callose, the triggering of particular plant defense responses was suggested as an additional mechanism for nematode antagonism. A more in-depth transcriptome analysis of *P. chlamydosporia* root colonization in barley, by means of an Affymetrix GeneChip, revealed an enrichment in genes involved in abiotic stress response, primarily those coding for heat shock proteins (82). An accumulation of genes associated with plant hormone biosynthesis, such as auxin, ethylene, and jasmonic acid (JA), and of genes related to effector-triggered immunity (ETI) and pattern-triggered immunity (PTI) was also observed. In cucumber plants, inoculated with the nematode antagonistic root-endophyte *T. asperellum* T203, an increased accumulation of lipoxygenase (*Lox1*), ethylene receptor 1 (*ETR1*) and constitutive triple response 1 gene B (*CTR1*) transcripts in roots and leaves indicated that the JA/ethylene-mediated induced defenses were detected (135). A combination of gene expression profiling, metabolic profiling, and genetic analyses on the root in the barley-*P. indica* interaction revealed a reduction in the available

free sugars. Simultaneously, there were changes in secondary metabolism, the accumulation of constituents in the regulation of signal perception and signal transduction, and the transcript levels of genes that correlate with membrane transport (127). In addition to this, an accumulation of genes involved in phytohormone metabolism, primarily gibberellin, auxin, and abscisic acid (ABA), was observed at particular stages of *P. indica* colonization, although salicylic acid (SA)-associated gene expression was reduced. It therefore seems that for *P. chlamydosporia*, *T. asperellum* T203, and *P. indica*, SA-mediated pathways are not involved in the induced defense responses.

The aforementioned studies were all done in the presence of the endophyte only, thus without an additional biotic stressor, such as plant-parasitic nematodes. Upon infection with the *M. incognita*, the presences of the endophytic *A. oligospora* strains increased the activity of plant defense-related enzymes in tomato leaves, such as PAL, polyphenol oxidase, chitinase, glucanase, superoxide dismutase, catalase, and peroxidases. Because these endophytes are restricted to the roots and the increase in activity was measured in the leaves, the plant defense responses can be considered systemic (142), although a potential priming effect by the endophyte could not be established because of the experimental setup. When Fo162-inoculated tomato plants were challenged with the whitefly *Trialeurodes vaporariorum*, PAL, PR1, and PR5 transcript accumulation was significantly increased within 24 hours, whereas LOX transcript accumulation was not changed (41). This indicates both a priming effect and the initiation of the SA-dependent systemic acquired resistance (SAR) (149) by the endophyte, which is restricted to the root system. For another nonpathogenic root-associated *F. oxysporum* strain Fo47, which can cause a systemic resistance to pathogenic *F. oxysporum* isolates in tomato (36, 47), the accumulation of PR1 transcripts and increased chitinase, β -1,3-glucanase, and β -1,4-glucosidase activity also point in the direction of SAR. Although not pathogenic in flax, Fo47 also caused a biphasic H₂O₂ accumulation, typical for a hypersensitive response, and Ca²⁺ spiking in the host plant (107). Studies on postinfection development of *M. arenaria* on susceptible and resistant peanut cultivars showed that the nematode development was delayed from 32 to 63 days, and HR-like responses were proposed to be responsible for the retarded development (114).

The induction of SA-dependent defense pathways may also lead to the accumulation of particular secondary metabolites synthesized by the plant that are detrimental for the nematode. Contrary to the noninoculated control, *N. coenophialum*-inoculated tall fescue plants generated metabolites that reduced motility on *P. scribneri*, an effect that could be reversed by removing the metabolites (6). There were several plant-derived phenolics reported that could lead to nematode paralysis (160), and recently a Musaceae phytoalexin, the phenylphenalenone anigorufone, which is synthesized by a banana cultivar that is resistant to *R. similis*, showed nematocidal activity upon ingestion by the nematode (68). Anigorufone proved to be the most abundant phenylphenalenone-type secondary metabolite present in the lesions created by *R. similis*, and the accumulation of other phenylphenalenones in the banana roots was also restricted to these lesions. Additionally, an increase in PAL activity, which is the initial enzyme of the phenylpropanoid biosynthesis pathway, is associated with the specific phenylpropanoid biosynthesis involved in defense and was significantly induced in *R. similis*-infected roots of the resistant banana cultivar Ykm5 (160). It is tempting to speculate that because Fo162 systemically reduces *R. similis* infection (153) and raises PAL transcript accumulation in response to a challenge, the endophyte initiates an increase of anigorufone accumulation in the banana roots up to toxic levels. In any case, the pathogenic *F. oxysporum* f. sp. *cubense*, the causal agent of the Panama disease, elicited anigorufone biosynthesis (89). Except for anigorufone, there is currently no information about nematocidal and nematostatic activities of phytoalexins in other plant species.

From these observations, one may conclude that SA-mediated defenses, the associated accumulation particular phytoalexins, and, additionally, HR-like responses are the most likely mechanisms

responsible for the endophyte-induced resistance against plant-parasitic nematodes. Nevertheless, split-root experiments in tomato showed that, when applied to the inducer side, both SA and methyl jasmonate can reduce *M. incognita* colonization at the responder side (133) and, when testing soil-borne antagonistic fluorescent pseudomonads, the systemic resistance induced against nematodes was reported to be independent of SA accumulation inside the roots (137). Therefore, cross talk between SA- and JA/ethylene-mediated defense pathways (152) must still be considered in the induced defense pathways against nematodes. Added to this, recent work in rice indicates that both pathways are part of a much more complex defense-regulating network, in which ABA and brassinosteroids act as repressors. There are indications that the nematodes themselves activate the ABA pathway to induce rice susceptibility (76). The influence by endophytes on this larger network has thus far not been studied.

Besides the SA- and JA/ethylene-mediated pathways, plants may have additional inducible defense pathways that can negatively affect nematode colonization and development. Deprivation of (homo)glutathione (GSH) in the roots negatively affected RKN colonization and development and caused an increase of the male-female ratio and a decrease in reproduction (12). These effects were all associated with alterations in the metabolism of the gall, resulting in a significant reduction in the accumulation of both soluble sugar and starch, which would explain the change in sex ratio, similar to what was found for cyst nematodes, and reduced fecundity. GSH, a low molecular weight thiol that can serve as an antioxidant, plays a positive role in the detoxification of xenobiotics and abiotic and biotic stress tolerance (43, 124, 161). Conversely, sufficient concentrations of (homo)GSH are necessary for root nodulation and therefore seem to be a prerequisite for the proper establishment of the symbiotic interaction between *Rhizobium* spp. and legumes (45). It is tempting to speculate that in order to establish and maintain root colonization, not only Fe14 but also other endophytic *Fusarium* spp., such as Fo162, are causing a reduction in (homo)GSH accumulation to within the plant's acceptable limits (45). A pathogenic *Fusarium culmorum* was able to reduce ascorbate and GSH levels in barley roots (60). Additionally, by regulating associated stress defense genes, GSH is involved in the resistance to oomycetes, bacterial pathogens, and insect herbivores (13, 110, 130).

In *Arabidopsis*, the *PAD2* gene codes for a c-glutamylcysteine synthetase, which is involved in the GSH synthesis and the *pad2-1* mutant, contains approximately 20% of the GSH found in wild-type plants (110). This mutant also accumulated lower levels of camalexin (51) and glucosinolates (130), and was more susceptible to the generalist insect *Spodoptera littoralis* (130) and hypersusceptible to the oomycete *Phytophthora porri* (123). The resistance to *P. porri* was independent of SA and JA/ethylene signaling. This pathway or, as suggested in the previous section, the cytokinin-mediated plant immunity (55) may also be induced by endophytes and responsible for nematode resistance.

QUANTITATIVE ANTAGONISM AND MICROBIAL COMPETITION

As indicated above, the identified endophytes that reduce nematode infection thus far provide only quantitative antagonism, and a percentage of the nematodes are still able to migrate, find their host, penetrate, establish, develop, and reproduce. This may be caused by the endophyte itself, which may not be capable of proliferating itself sufficiently inside the root system, by a weak priming of the plant, or both. The plant (genotype) too may have its limitations, such as being incapable of sufficiently accommodating the endophyte or not being able to mount effective direct or primed defense responses to the nematode. Furthermore, because it can be assumed the antagonism is very ancient (76), the nematode population may have adapted to a certain extent and is able to counteract this antagonism along similar lines found for fungal pathogens, such as

detoxification of plant- or endophytic-derived compounds (35, 131) or, to extrapolate the findings on hormone balances and immunity (53, 81), active repression of the endophyte-induced defense pathways by the nematode.

Because most of the screening for nematode antagonistic endophytes is done under nonaxenic conditions, interactions with other microorganisms may also interfere. That this may be an issue was illustrated through work in which individual antagonists were pooled in one plant, with the goal to combine complementary modes-of-action initiated by each individual antagonist in order to obtain an even higher level of resistance. Because the actual mechanisms of the antagonism are still poorly understood, they may nevertheless still overlap or interfere. A combined application of the endophytic egg parasitic fungus *P. lilacinus* strain 251 and Fo162 showed a better control of *R. similis* in banana when compared with the application of each antagonist individually (98). However, when the AM fungus *Glomus coronatum* and Fo162 were inoculated together, no improvement of RKN control was observed, although each organism individually antagonized *M. incognita* in tomato (34). A triple split-root experiment in which Fo162 and the endophytic antagonistic bacterium *Rhizobium etli* strain R12 (R12) were individually applied to a separate inducer side showed no further reduction in RKN infection at the responder side when compared with the application of each individual antagonist (95). In this case, R12 also systemically reduced the colonization of Fo162, as was determined in an additional split-root experiment. Such a reduction in Fo162 colonization was not observed in the combination with *P. lilacinus* (98). This indicates that endophytes can also affect each other, even systemically, thus influencing the overall control of nematode infections. This incompatibility may not be limited to nematode antagonists alone and, under natural conditions, the in planta coexistence with any other endophytic or pathogenic microorganism may lead to a decrease in the overall antagonistic activity toward nematodes. In this respect, the role of the plant in mediating this competition is not at all clear. Plants may very well prioritize their defenses (152), thus facilitating the proliferation of endophytes that are most useful in coping with the most harmful adverse elements under the given growth conditions. Such habitat-adapted symbiosis with endophytes was described for coping with abiotic stress conditions. In coastal regions, dune grass (*Leymus mollis*) was found to harbor a particular *F. culmorum* endophyte that supported the plant in tolerating salt stress (121). In panic grass (*Dichanthelium lanuginosum*) growing on geothermal soils of Yellowstone National Park, *Curvularia protuberata* conferred heat tolerance (118). Thus far, nothing is known about whether or not plants can exchange one endophyte for another to adapt to changing adverse conditions.

CONCLUDING REMARKS AND PROSPECTS

There is ample evidence that various endophytic fungi can support plants in resisting plant-pathogenic nematodes. The accumulated data give some clues about the machineries involved, although they do not all point in the same direction. In particular, the role of endophytic nematocidal and nematostatic metabolites, phytoalexins, and other induced plant defense responses are far from being resolved. A better understanding of the mechanisms behind this antagonism is important for the application of the endophytes or specific endophyte-derived compounds in the field and the selection of host plant genotypes that do respond better to endophytes. Advances in molecular, biochemical, analytical, and methodological approaches will facilitate the unraveling of the individual mechanisms in the future. The genome of the endophyte Fo162 has now been fully sequenced (R. Mann, J. Eschweiler, A. Elashry, A. Schouten, unpublished results). This is valuable for determining biosynthetic pathways and for genome and transcriptome studies between other nonpathogenic and pathogenic *F. oxysporum* isolates. It will also help us to further understand the biological meaning of the endophytic continuum as a concept. The relevant effectors for being an

endophyte with particular beneficial properties, such as antagonizing plant-parasitic nematodes, can be characterized, also with the help of mutant analysis. The power of genome comparisons is illustrated by the characterization of *F. oxysporum* lineage-specific chromosomes, which are associated with pathogenicity on tomato (90). That *Arabidopsis* can be used as a model system for studying the various plant-nematode-endophyte interactions (30, 97) is in this respect another asset, particularly because of the availability of a vast collection of well-characterized mutants. However, close attention must be paid to the direct effects on the endophyte itself. In addition, by merging state-of-the-art microscopical and biochemical techniques, the presence of constituents in roots, nematodes, or even individual cells within roots or nematodes can be assessed more easily than ever before, as was demonstrated with the matrix-free laser desorption/ionization Fourier transform ion cyclotron resonance mass spectrometric imaging (LDI-FT-ICR-MSI) technique (69). The description of this technique in itself already perfectly illustrates that multidisciplinary research forms the key in further dissecting tripartite interactions among plants, endophytes, and nematodes.

SUMMARY POINTS

1. In every ecosystem, endophytic fungi are encountered in virtually every plant. However, their beneficial role in the plant's development is often difficult to establish.
2. Several fungal endophytes belonging to various species have been shown to antagonize plant-parasitic and entomopathogenic nematodes. This feature may be valuable for developing sustainable nematode control practices in agriculture.
3. The mechanism by which this antagonism operates is multifactorial. Depending on the species, the endophyte affects nematodes by directly repelling or attacking them and kills nematodes by means of (toxic) constituents or enzymes. By eliciting or priming plant defense responses, endophytes can indirectly antagonize nematodes as well. In addition, the combination of biosynthetic pathways of the plant and the fungal endophyte may also result in novel bioactive compounds directed toward nematodes.
4. The endophytic antagonism toward nematodes is quantitative. This may be caused by restrictions in the establishment of the proper endophyte inside the plant, the potential competition between nematode antagonistic endophytes and endophytes with other beneficial competences, and the intrinsic limitations of the plant in priming or raising defenses against nematodes upon colonization by the endophyte.
5. Newer and more refined techniques make it possible to further identify the currently unknown factors that play a role in endophytic antagonism toward nematodes in plants, thus benefiting both fundamental and applied research regarding endophytic antagonism toward nematodes.

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