

The Hidden World within Plants: Ecological and Evolutionary Considerations for Defining Functioning of Microbial Endophytes

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SUMMARY

All plants are inhabited internally by diverse microbial communities comprising bacterial, archaeal, fungal, and protistic taxa. These microorganisms showing endophytic lifestyles play crucial roles in plant development, growth, fitness, and diversification. The increasing awareness of and information on endophytes provide insight into the complexity of the plant microbiome. The nature of plant-endophyte interactions ranges from mutualism to pathogenicity. This depends on a set of abiotic and biotic factors, including the genotypes of plants and microbes, environmental conditions, and the dynamic network of interactions within the plant biome. In this review, we address the concept of endophytism, considering the latest insights into evolution, plant ecosystem functioning, and multipartite interactions.

INTRODUCTION

Endophytes are microorganisms that spend at least parts of their life cycle inside plants. Endophyte definitions have changed in the past years and expectedly will evolve further over the coming years. The term “endophyte” has commonly been used for fungi living inside plants, but later researchers realized that interior parts of plants could be colonized by bacteria as well (1, 2). Plants do not live alone as single entities but closely associate with the microorganisms present in their neighborhood, and especially with those living internally. The emergence of the concept of the “plant microbiome,” i.e., the collective genomes of microorganisms living in association with plants, has led to new ideas on the evolution of plants where selective forces do not act merely on the plant genome itself but rather on the whole plant, including its associated microbial community. Lamarckian concepts of acquired heritable traits may be explained via the hologenome concept by vertical transmission of valuable traits provided by endophytes to plants (3).

The most common definition of endophytes is derived from the practical description given in 1997 by Hallmann and coauthors (2), who stated that endophytes are “. . . those (bacteria) that can be isolated from surface-disinfested plant tissue or extracted from within the plant, and that do not visibly harm the plant.” This definition has been valid for cultivable species in most laboratories in the world over the past 2 decades. However, due to the suspected lack of adequate elimination of nucleic acids after disinfection of plant surfaces, this definition appeared to be less suitable for noncultured species upon the introduction of molecular detection techniques in endophyte research (4).

Conceptual aspects related to the nature of endophytes are

under dispute. For instance, must plant pathogens be considered endophytes or not, even when they have lost their virulence (5)? Recently, a typical bacterial group of endophytes beneficial to plants, the group of fluorescent pseudomonads, turned out to be detrimental to leatherleaf ferns under specific conditions (6). This indicates that potential plant mutualists can become deleterious for their hosts. Endophytes should not be harmful to the plant host, but what about harmfulness to other species, for instance, when particular bacteria that colonize internal compartments of plants are harmful to humans (7)?

The most common endophytes are typed as commensals, with unknown or yet unknown functions in plants, and less common ones are those shown to have positive (mutualistic) or negative (antagonistic) effects on plants (2). However, these properties are often tested in a single plant species or within groups of closely related plant genotypes, but rarely over a taxonomically wide spectrum of plant species. Also, the environmental conditions wherein plant-endophyte interactions are studied are often rather narrow. Furthermore, interactions between members of the endophyte community have rarely been investigated. A few studies demonstrated that interactions between taxonomically related microbial endophytes can shift whole populations inside the plant (8, 9). Bacterial and fungal endophytic communities are commonly investigated separately, but the interaction between both groups inside plants can become a fascinating new field in endophyte research (10).

Studies of plant-endophyte interactions are commonly based on controlled, optimized conditions for growth of host plants and seldom based on variable, field-realistic conditions. Effects ascribed to endophytes in healthy plants might change when host plants are grown under less favorable, or even stressful, conditions. In conclusion, our current understanding of endophytes is built on a rather small set of experimental conditions, and more varied experimental settings would be required for deeper insight into endophyte functioning. Because of this and the general preference to investigate microbial species that are relatively easy to cultivate, our knowledge of the ecology and interactions of endophytes in plants is still biased.

New developments in high-throughput technologies, such as next-generation sequencing, permit the investigation of complex microbiomes and will facilitate larger sample sizes and encourage deeper analyses of microbial communities (11). The new “omics” approaches are valuable tools for exploring, identifying, and characterizing the contributions of genetic and metabolic elements involved in the interactions between host plants and endophytes.

For instance, metagenome sequencing has revealed important functions required for survival of bacterial endophytes inside plants (12), and metabolome analysis demonstrated the effects of beneficial endophytes on primary metabolites of plants (13). The combination of cultivation-independent and improved cultivation technologies will allow the exploration of hitherto uncultured groups living in association with plants (14, 15). In addition, the locations of endophytes in different plant compartments are disputable (16), but powerful image analyses can provide information about the exact colocalization within plant tissues and about physical contacts between different microbial groups (17–19). We are reaching a pivotal point in our perception of endophytes, and we expect that technical innovations in microbial detection will soon drastically change our concepts of endophytes as living entities colonizing internal plant compartments.

In this paper, we present a historical overview of the endophyte research leading to the current understanding of endophytes. The state of science for defined groups of endophytes is described in succeeding sections, based on the vast number of peer-reviewed publications on endophytes, which have been growing exponentially over the last 3 decades. Furthermore, we elaborate the expected impacts of novel technologies on endophyte research. It is our purpose to revisit current concepts on endophytes and to assess directions for new research on microbial endophytes based on the latest technological developments.

HISTORY OF ENDOPHYTE DEFINITIONS

The German botanist Heinrich Friedrich Link was the first to describe endophytes, in 1809 (20). At that time, they were termed “*Entophytæ*” and were described as a distinct group of partly parasitic fungi living in plants. Since then, many definitions have evolved; for a long time, they mostly addressed pathogens or parasitic organisms, primarily fungi (21–23). Only Béchamp described so-called microzymas in plants, referring to microorganisms (24). Generally, in the 19th century, the belief was that healthy or normally growing plants are sterile and thus free of microorganisms (postulated by Pasteur; cited in reference 25). Nevertheless, Galippe reported the occurrence of bacteria and fungi in the interior of vegetable plants and postulated that these microorganisms derive from the soil environment and migrate into the plant, where they might play a beneficial role for the host plant (26, 27). Other studies in the late 19th century and the beginning of the 20th century confirmed the occurrence of beneficial microorganisms within plants (28, 29). Nevertheless, contrasting views on the existence of plant-beneficial endophytes prevailed at that time (28, 30–34). Nowadays, it is a well-established fact that plants are hosts for many types of microbial endophytes, including bacteria, fungi, archaea, and unicellular eukaryotes, such as algae (35) and amoebae (36).

An important discovery was made in 1888 by the Dutch microbiologist Martinus Willem Beijerinck, who isolated root nodule bacteria in pure culture from nodules of Leguminosae plants and showed that these isolates, which were later classified as *Rhizobium leguminosarum* (37), were capable of fixing atmospheric nitrogen (38). At the same time, Hermann Hellriegel and Hermann Wilfarth reported mineral N independence of leguminous plants, as well as the importance of symbiotic nitrogen fixation by rhizobia (39). Albert Bernhard Frank reported another important mutualistic symbiosis, i.e., the living together of unlike organisms (40), between roots of trees and underground fungi (41). He

coined the term “mycorrhiza” to describe the interaction, which literally means “fungus roots.”

More recently, in 1991, Orlando Petrini defined endophytes as “all organisms inhabiting plant organs that at some time in their life cycle can colonize internal plant tissues without causing apparent harm to their host” (42). Since then, many definitions have been formulated (2, 43–48), essentially all pertaining to microorganisms which for all or part of their life cycle invade tissues of living plants without causing disease. Although this endophyte definition has been the basis of many studies and might be a pragmatic approach to distinguish between endophytes and pathogens, it has some drawbacks and raises some questions.

First, this definition is more suitable for cultivated endophytes, as only with those is it possible to assess phytopathogenicity. However, in most cases, pathogenicity assays are not performed, or they are performed with only one plant species, although pathogenicity might occur with a different plant genotype or under different conditions. Second, it is well known that some bacteria may live as latent pathogens within plants and become pathogenic under specific conditions (6) or are pathogens of other plants. Third, it has been shown that bacterial strains belonging to a well-known pathogenic species of a specific plant host may even have growth-promoting effects on another plant (49, 50). These findings demonstrate that it is not trivial to clearly distinguish a non-pathogenic endophyte from a pathogen and that properties such as pathogenicity or mutualism may depend on many factors, including plant and microbial genotype, microbial numbers, and quorum sensing or environmental conditions. With cultivation-independent analyses, it is now even more difficult to assess the pathogenicity of individual microbiome members. In conclusion, we question the currently applied definition of endophytes and claim that the term “endophyte” should refer to habitat only, not function, and therefore that the term should be more general and include all microorganisms which for all or part of their lifetime colonize internal plant tissues.

PLANT-MICROBE SYMBIOSES

Different groups of bacteria and fungi interact with higher plants. Genetic links between the association of plants with arbuscular mycorrhizal fungi (AMF) and root nodule symbioses have been found (51–53), suggesting that at least segments of bacterial and fungal endophytic populations coevolved with each other and with their host. Mutualistic interactions leading to adaptive benefits for both partners occasionally evolved to even more complex forms, in which more than two partners were involved (10).

Evolution of Plant-Fungus Symbioses

Plant-fungus symbioses are known to have occurred during early colonization of land by terrestrial plants (54). The fungal group *Glomeromycota* has for a long time been the prime candidate for interaction with the first terrestrial plants, in the Ordovician era, but members of the *Mucoromycotina* are also speculated to have had symbiotic interactions with the first terrestrial plants (55). The association between AMF and plants evolved as a symbiosis, facilitating the adaption of plants to the terrestrial environment (56). The oldest known fossils representing terrestrial fungi with properties similar to those of AMF were collected from dolomite rocks in Wisconsin and are estimated to be 460 million years old, originating from the Ordovician period (54). It was therefore assumed that terrestrial AMF already existed at the time when bryo-

phyte-like, “lower” plants covered the land. All other plant-AMF interaction types, such as ectomycorrhiza and orchid and ericoid mycorrhiza, appeared later and are considered to be derived from the first interactions between AMF and the first terrestrial plants (57).

It is assumed that no tight interactions between plants and fungi occurred initially but that, due to nutritional limitations, interactions between both partners evolved (57). It is still unknown whether the first AMF were already mutualistic symbionts or whether mutualistic lifestyles evolved from pathogenic forms. The internal spaces of plants became important habitats for plant-colonizing fungi. Specific tissue layers, such as the endodermis and exodermis, evolved, forming the borders of cortex cells surrounding fungi internalized in the roots (57). This finally resulted in the formation of arbuscules, which are typical structures in plant-AMF interactions. AMF became more dependent on their host for energy sources and adopted an obligate life cycle. On the other hand, intraradical hyphae increased the total root surface area of the host plant, allowing substantially more nutrient (P) uptake from the soil environment. As evolution progressed, more extreme forms of plant-fungus interactions appeared, such as mycoheterotrophic plants, i.e., plants that fully exploit their fungal counterparts during interaction (58).

Evolution of Plant-Bacterium Symbioses

The best-described plant-bacterium interaction is the one between leguminous plants and rhizobia. The interactions of nitrogen-fixing bacteria belonging to the genera *Azorhizobium*, *Bradyrhizobium*, *Ensifer*, *Mesorhizobium*, *Rhizobium*, and *Sinorhizobium* (collectively called “rhizobia”; for a full list of genera, see <http://www.rhizobia.co.nz/taxonomy/rhizobia>) are capable of inducing differentiation in root nodule structure, as demonstrated in *Fabaceae* and *Parasponia* plants (60). Typical symptoms in roots of leguminous plants infected by rhizobia are curling of root hairs and the appearance of infection threads and, finally, nodule primordia in the inner root layers—these are all processes mediated by signal exchange between plants and rhizobia (for a review, see reference 61). In primordium cells, the bacteria become surrounded by the plant membrane, and together, the bacteria and plant structure form the symbiosome, in which atmospheric nitrogen is fixed and transferred in exchange for carbohydrates (62). Symbiosomes have a structure similar to that of mycorrhizal arbuscules, which are also surrounded by a plant membrane. It is interesting that a number of legume-nodulating rhizobial strains form endophytic associations with monocotyledonous plants, such as rice (63), maize (64), and sugarcane (65), and dicotyledonous plants, such as sweet potato (66). Although nodule primordia were not observed, rhizobial *nifH* transcripts were found inside roots of rice and sugarcane plants (12, 65). The contribution of rhizobium-assimilated nitrogen to the total nitrogen pool in nonleguminous plants is still a matter of debate (67).

Recent studies revealed that the nature of the association of both AMF and rhizobia with host plant species can be mutualistic, parasitic, or nonsymbiotic (68, 69). A meta-analysis demonstrated that the plant response to AMF depends on various factors, most importantly the host plant type and N fertilization (69). Apart from mutualistic rhizobia, parasitic strains which infect legumes but fix little or no nitrogen have been reported (68). The rhizobium-legume symbiosis seems to be characterized by a continuum of different types of symbiotic interactions, in many cases depen-

dent on the presence of symbiotic genes, frequently located on plasmids, needed for the mutualistic interaction (70).

ENDOPHYTE DIVERSITY

Prokaryotic Endophytes

We present an overview of prokaryotic endophytes reported to date, based on a curated database (see Data Sets S1 and S2 in the supplemental material) comprising all currently available 16S rRNA gene sequences assigned to endophytes (published in peer-reviewed journals indexed to the PubMed or Web of Science databases and deposited in the International Nucleotide Sequence Database Collaboration repository, as of 1 March 2014). Only sequences longer than 300 bp and from studies that applied well-established surface sterilization procedures, such as the application of sodium hypochlorite (NaOCl) or mercury chloride (HgCl₂), were included. The database comprises 4,146 16S rRNA gene sequences from isolates (56%) and 3,202 16S rRNA gene sequences from uncultured organisms (44%). Sequences from earlier next-generation high-throughput sequencing technologies (e.g., 454 pyrosequencing) were able to produce only relatively short nucleotide stretches (i.e., <300 bp), which limits the discriminatory power for classification of different taxonomic groups, and thus were not included in our database.

Prokaryotic endophytes considered in this database are diverse and comprise 23 recognized and candidate phyla (2 from *Archaea* and 21 from *Bacteria*) (Table 1; see Fig. S1 in the supplemental material). Despite this remarkable diversity, more than 96% of the total number of endophytic prokaryotic sequences ($n = 7,348$) are distributed among four bacterial phyla (54% *Proteobacteria*, 20% *Actinobacteria*, 16% *Firmicutes*, and 6% *Bacteroidetes*). These phyla have also been reported to be dominant in the plant environment (71, 72). The database comprises only a few ($n = 29$) sequences from *Archaea*, which were mainly detected in coffee cherries (73), rice and maize roots (74, 75), and the arctic tundra rush *Juncus trifidus* (76).

Most of the prokaryotic endophytes (26%) could be assigned to the *Gammaproteobacteria*, including 56 recognized and 7 unidentified genera as well as the “*Candidatus Portiera*” genus (see Data Set S1 and Fig. S2 in the supplemental material). It should be noted that *Gammaproteobacteria* also comprise a large number of genera and species which are known as phytopathogens (77, 78). Endophytic *Gammaproteobacteria* are largely represented by a few genera: *Pseudomonas*, *Enterobacter*, *Pantoea*, *Stenotrophomonas*, *Acinetobacter*, and *Serratia* (>50 sequences each) (see Fig. S2). Members of the genus *Enterobacter* associate with diverse organisms, and their ecological relationships range from mutualism to pathogenesis. For instance, four species of *Enterobacter* in plants have been described as opportunistic pathogens, whereas many others (at least five) are beneficial to the host (79), including a monophyletic clade that was recently named *Kosakonia* (80). The nature of the interactions of other members of the *Gammaproteobacteria*, including *Pseudomonas*, *Pantoea*, and *Stenotrophomonas* species, is similar to that for *Enterobacter*, with few species described as plant pathogens and many others described as plant mutualists. Similarly, the *Alphaproteobacteria* encompass a large number (18%) of endophytic sequences, belonging to 57 recognized and 14 unidentified genera as well as the “*Candidatus Liberibacter*” genus (see Data Set S1 and Fig. S3). Most of the sequences can be assigned to the genera *Rhizobium* and *Bradyrhi-*

TABLE 1 Summary of the endophytic data set from all peer-reviewed publications with prokaryotic 16S rRNA gene sequences^a

Phylogenetic affiliation ^b	No. of sequences	% of sequences
Bacteria	7,319	
<i>Acidobacteria</i>	53	0.72
<i>Actinobacteria</i>	1,461	19.88
<i>Armatimonadetes</i>	6	0.08
<i>Bacteroidetes</i>	462	6.29
GOUTA4 ^c	1	0.01
OD ^c	6	0.08
TM7 ^c	2	0.03
<i>Chlamydiae</i>	8	0.11
<i>Chlorobi</i>	5	0.07
<i>Chloroflexi</i>	3	0.04
<i>Cyanobacteria</i>	102	1.39
<i>Deinococcus-Thermus</i>	7	0.1
<i>Elusimicrobia</i>	1	0.01
<i>Firmicutes</i>		
<i>Bacilli</i>	1,132	15.41
<i>Clostridia</i>	68	0.93
<i>Fusobacteria</i>	3	0.04
<i>Nitrospirae</i>	3	0.04
<i>Planctomycetes</i>	5	0.07
<i>Proteobacteria</i>		
Alpha-	1,337	18.2
Beta-	736	10.02
Delta-	26	0.35
Epsilon-	3	0.04
Gamma-	1,878	25.56
<i>Spirochaetae</i>	3	0.04
<i>Tenericutes</i>	2	0.03
<i>Verrucomicrobia</i>	6	0.08
Archaea	29	
<i>Euryarchaeota</i>	23	0.31
<i>Thaumarchaeota</i>	6	0.08
Total	7,348	

^a Endophytic sequences with >300 bp were retrieved from peer-reviewed manuscripts available in the ISI Web of Science and PubMed databases (as of 1 March 2014).

^b Based on comparison with the small-subunit rRNA SILVA database (version 115) (372) by using the SINA aligner (364).

^c Candidate division phyla.

zobium, known for their N₂-fixing symbioses with legumes, and *Methylobacterium* and *Sphingomonas* (>50 sequences each) (see Fig. S3). *Methylobacterium* is capable of growth on methanol as the sole source of carbon and energy and has been hypothesized to potentially dominate the phyllosphere environment (81). The *Betaproteobacteria* sequences (10%) comprise 53 recognized and 10 unidentified genera of endophytes (see Data Set S1), mainly belonging to *Burkholderia*, *Massilia*, *Variovorax*, and *Collimonas* (≥40 sequences each) (see Fig. S4). *Burkholderia* strains have the potential to colonize a wide range of hosts and environments (82), suggesting a great metabolic and physiological adaptability of endophytes belonging to this genus.

Among Gram-positive endophytes, the class *Actinobacteria* (20%) comprises diverse endophytes belonging to 107 recognized and 15 unidentified genera (see Data Set S1 in the supplemental material). Most of the sequences group with the genera *Streptomyces*, *Microbacterium*, *Mycobacterium*, *Arthrobacter*, and *Curto-*

bacterium (>50 sequences each) (see Fig. S5). Members of the genus *Streptomyces* are well known for their capacity to synthesize antibiotic compounds (83). The class *Bacilli* (15%) comprises 25 recognized and 2 unidentified genera of endophytes (see Data Set S1). The genera *Bacillus*, *Paenibacillus*, and *Staphylococcus* have more than 100 sequences assigned to them (see Fig. S6). Within the genus *Bacillus*, the species *Bacillus thuringiensis* is well known for its production of parasporal crystal proteins with insecticidal properties (84).

Overall, most bacterial endophytes belong to mainly four phyla, but they encompass many genera and species. Their functions cannot be assigned clearly to taxonomy and seem to depend on the host and environmental parameters.

Eukaryotic Endophytes

A data set of eukaryotic endophytic full-length internal transcribed spacer (ITS) regions was also built for this study (see Data Set S3 in the supplemental material). A total of 8,439 sequences were retrieved from the National Center for Biotechnology Information (NCBI) nucleotide database (Table 2 shows the details of data retrieval and analysis; data were current as of 1 August 2014). Endophytes mainly belong to the *Glomeromycota* (40%), *Ascomycota* (31%), *Basidiomycota* (20%), unidentified phyla (8%), and, to a lesser extent, *Zygomycota* (0.1%) (Table 2).

The phylum *Glomeromycota* only comprises endophytes known as arbuscular mycorrhizal fungi (AMF) (85) (see Data Set S3 in the supplemental material). Most of the eukaryotic endophytes (39%) can be assigned to the class *Glomeromycetes*. All members of this class form ubiquitous endosymbioses with most land plants and are of undeniable ecological and economic importance (86–88). AMF of the genera *Glomus* and *Rhizophagus* form obligate symbioses with a wide variety of host plants from the subkingdom *Embryophyta* (86). Among the *Ascomycota*, a large number of endophytes are identified in the class *Dothideomycetes* (15%). Besides endophytes, many members of the *Dothideomycetes* class are necrotrophic plant-pathogenic fungi, which are remarkable because of their production of host-specific toxins, such as phytotoxic metabolites and peptides that are biologically active only against a particular plant species (89–92). Overall, this class contains many species of the genera *Alternaria* and *Epicoccum* comprising endophytes (see Data Set S3). Although *Alternaria brassicae* is considered an opportunistic plant pathogen (93), it is frequently detected in high abundance in healthy plants (94, 95). Many members of the class *Sordariomycetes* (9%) are endophytes, such as species of the genera *Balansia*, *Epichloë*, *Nemania*, *Xylaria*, and *Colletotrichum*, but this class is also well known for phytopathogenic members, such as *Cryphonectria parasitica* (the causal agent of chestnut blight), *Magnaporthe grisea* (rice blast), *Ophiostoma ulmi* and *Ophiostoma novo-ulmi* (Dutch elm disease), and *Fusarium*, *Verticillium*, and *Rosellinia* species (96).

Among the *Basidiomycota* (Table 2), the class *Agaricomycetes* (18%) contains a large number of endophytes, mainly mushroom-forming (basidiome) fungi causing wood decay, white and brown rot saprotrophs, and the beneficial ectomycorrhiza (EMC) symbionts (97). Furthermore, members of the order *Sebacinales* form mycorrhizal symbioses with a broad range of plants, including woody plants and members of the families *Orchidaceae* and *Ericaceae* and the division *Marchantiophyta* (98). Additional assigned classes containing endophytes are *Atractiellomycetes*, *Cystobasidiomycetes*, *Microbotryomycetes*, and *Tremellomycetes*

TABLE 2 Summary of the endophytic data set from all peer-reviewed eukaryotic full-length ITS sequences (as of 1 August 2014)^a

Taxonomic assignment ^b	No. of sequences	% of sequences
Total	8,439	
<i>Ascomycota</i>	2,610	30.92
<i>Archaeorhizomycetes</i>	2	0.02
<i>Dothideomycetes</i>	1,272	15.07
<i>Eurotiomycetes</i>	54	0.64
<i>Incertae sedis</i>	2	0.02
<i>Lecanoromycetes</i>	5	0.06
<i>Leotiomycetes</i>	171	2.03
<i>Orbiliomycetes</i>	0	0
<i>Pezizomycetes</i>	112	1.33
<i>Saccharomycetes</i>	11	0.13
<i>Sordariomycetes</i>	785	9.30
Unidentified	196	2.32
<i>Basidiomycota</i>	1,712	20.3
<i>Agaricomycetes</i>	1,560	18.49
<i>Atractiellomycetes</i>	26	0.31
<i>Cystobasidiomycetes</i>	3	0.04
<i>Exobasidiomycetes</i>	0	0
<i>Microbotryomycetes</i>	23	0.27
<i>Pucciniomycetes</i>	1	0.01
<i>Tremellomycetes</i>	30	0.36
<i>Ustilaginomycetes</i>	0	0
Unidentified	69	0.82
<i>Glomeromycota</i>	3,390	40.17
<i>Glomeromycetes</i>	3,294	39.03
Unidentified	96	1.14
<i>Zygomycota</i>		
<i>Incertae sedis</i>	5	0.06
Unidentified	722	8.56

^a Fungal ITS sequences were retrieved from the NCBI nucleotide database by using the following search strings for the endophytic data set: “Endophyt*[ALL] AND nuccore_PubMed[Filter] AND internal[Title]” and “Mycorrhiza*[ALL] AND nuccore_PubMed[Filter] AND internal[Title].” Full-length ITS (ITS1, 5.8S, and ITS2 regions) sequences were extracted using ITSx (365) and assigned to operational taxonomic units (OTUs; definition set at 97% sequence similarity) with UCLUST (366), using the QIIME pipeline (367).

^b Based on comparison with the UNITE fungal ITS reference database (version 6) (368), using the QIIME pipeline (367).

(see Data Set S3 in the supplemental material). Similar to the case for bacterial endophytes, various taxa comprise known phytopathogens and strains without known pathogenic effects, indicating that the functions of endophytic fungi also cannot necessarily be linked to taxonomy.

LIFESTYLES OF ENDOPHYTES

Degrees of Intimacy between Plants and Endophytes

Microorganisms can be strictly bound to plants and complete a major part or even their entire life cycle inside plants. Microorganisms requiring plant tissues to complete their life cycle are classified as “obligate.” Well-documented examples of obligate endophytes are found among mycorrhizal fungi and members of the fungal genera *Balansia*, *Epichloë*, and *Neotyphodium*, from the family *Clavicipitaceae* (*Ascomycota*) (99, 100). On the other ex-

treme are “opportunistic” endophytes that mainly thrive outside plant tissues (epiphytes) and sporadically enter the plant endosphere (101). Among these are rhizosphere-competent colonizers, such as bacteria of the genera *Pseudomonas* and *Azospirillum* and fungi of the genera *Hypocrea* and *Trichoderma* (102–105). It is interesting that endophytes, which are transmitted vertically via seeds, are often recovered as epiphytes, suggesting that various endophytes might also colonize surrounding host plant environments (106, 107). Between these two extremes is an intermediate group, which comprises the vast majority of endophytic microorganisms, the so-called “facultative” endophytes. Whether facultative endophytes use the plant as a vector for dissemination or are actively selected by the host is still a matter of debate (107–110). However, facultative endophytes consume nutrients provided by plants, which would in fact reduce the ecological fitness of the host plant. This point is therefore often used as an argument that the so-called facultative endophytes must be mutualists in plants, even if the details of the interaction are unclear.

Overlaps exist between these three groups; thus, these categories must be considered “marking points” within the continuum of colonization strategies existing among endophytes. Independent of class, the microbial species thriving inside plant tissues are ecologically fit to survive and to proliferate under the local conditions of the plant interior, and aspects of survival are discussed later.

COLONIZATION OF THE ENDOSPHERE

Colonization Behavior of Fungal Endophytes

Successful colonization by endophytes depends on many variables, including plant tissue type, plant genotype, the microbial taxon and strain type, and biotic and abiotic environmental conditions. Different colonization strategies have been described for clavicipitaceous and nonclavicipitaceous endophytes (111, 112). Species of the *Clavicipitaceae*, including *Balansia* spp., *Epichloë* spp., and *Claviceps* spp., establish symbioses almost exclusively with grass, rush, and sledge hosts (47, 113), in which they may colonize the entire host plant systemically. They proliferate in the shoot meristem, colonizing intercellular spaces of the newly forming shoots, and can be transmitted vertically via seeds (113). Some *Neotyphodium* and *Epichloë* species may also be transmitted horizontally via leaf fragments falling on the soil (114). At the stage of inflorescence development, the mycelium of *Neotyphodium* can also colonize ovules and be present during infructescence development in the scutellum and the embryo, as demonstrated for *Lolium perenne* (115). When the inflorescence of the grass host develops, *Epichloë* can also grow over the developing inflorescence and form stromata, which can be differentiated sexually with the help of *Botanophila* flies (116).

Based on colonization characteristics, Rodriguez et al. (117) classified clavicipitaceous endophytes as class 1 fungal endophytes. Fungi colonizing above- and below-ground plant tissues, i.e., the rhizosphere, endorhiza, and aerial tissues (118), and being horizontally and/or vertically transmitted (119) were grouped as class 2 fungal endophytes (117). Class 3 endophytes were defined to contain mostly members of the *Dikaryomycota* (*Ascomycota* or *Basidiomycota*), which are particularly well studied in trees, but also in other plant taxa and in various ecosystems (120–126). Members of this class are mostly restricted to aerial tissues of various hosts and are horizontally transmitted (127, 128). Class 4

endophytes comprise dark, septate endophytes, which, similar to mycorrhizal fungi, are restricted to roots, where they reside inter- and/or intracellularly in the cortical cell layers (129).

Colonization Behavior of Bacterial Endophytes

Many bacterial endophytes originate from the rhizosphere environment, which attracts microorganisms due to the presence of root exudates and rhizodeposits (130, 131). Mercado-Blanco and Prieto (132) suggested that the entry of bacterial endophytes into roots occurs via colonization of root hairs. To a certain extent, stem and leaf surfaces also produce exudates that attract microorganisms (130). However, UV light, the lack of nutrients, and desiccation generally reduce colonization of plant surfaces, and only adapted bacteria can survive and enter the plant via stomata, wounds, and hydathodes (130, 133). Endophytes may also penetrate plants through flowers and fruits via colonization of the anthesis and carpophere (18, 130).

Depending on the strain, various colonization routes have been described, and specific interactions have been suggested (133, 134). Several of these routes involve passive or active mechanisms enabling bacteria to migrate from the rhizoplane to the cortical cell layer, where the plant endodermis represents a barrier for further colonization (130, 135). For bacteria that can penetrate the endodermis, the xylem vascular system is the main transport route for systemic colonization of internal plant compartments (134), whereas others colonize intercellular spaces locally. Bacteria have been shown to colonize xylem vessels, and the sizes of the holes of the perforation plates between xylem elements are sufficiently large to allow bacterial passage (130, 134, 136–138). However, vertical spread of bacteria through plants may take several weeks (139), and it is unclear why bacterial endophytes progress so slowly in the vascular system. Bacteria might even migrate to reproductive organs of Angiospermae plants and have been detected in the inner tissues of flowers (epidermis and ovary), fruits (pulp), and seeds (tegument) of grapevines (18) and in pumpkin flowers (140), as well as in the pollen of pine, a Gymnospermae plant (141). Suitable niches for colonization by bacterial endophytes have been described for different plant taxonomic groups, including Bryophytes, Pteridophytes, Gymnospermae, and Angiospermae (17, 130, 142) (Fig. 1). Overall, it is not known whether endophytes need to reach a specific organ or tissue for optimal performance of the functions which have been identified for endophytes.

FUNCTIONS OF ENDOPHYTES

Some endophytes have no apparent effects on plant performance but live on the metabolites produced by the host. These are termed commensal endophytes, whereas other endophytes confer beneficial effects to the plant, such as protection against invading pathogens and (arthropod) herbivores, either via antibiosis or via induced resistance, and plant growth promotion (Fig. 2). A third group includes latent pathogens (143). Generally, endophytes can have neutral or detrimental effects to the host plant under normal growth conditions, whereas they can be beneficial under more extreme conditions or during different stages of the plant life cycle. For example, the fungus *Fusarium verticillioides* has a dual role both as a pathogen and as a beneficial endophyte in maize (144). The balance between these two states is dependent on the host genotype, but also on locally occurring abiotic stress factors that reduce host fitness, resulting in distortion of the delicate balance

and in the occurrence of disease symptoms in the plant and production of mycotoxins by the fungus (144). However, beneficial effects have also been demonstrated, e.g., strains of the endophytic fungus *F. verticillioides* suppress the growth of another pathogenic fungus, *Ustilago maydis*, protecting their host against disease (145).

Plant Growth Promotion and Protection against Biotic and Abiotic Stresses

ISR and production of antibiotic secondary metabolites. Carroll (111) suggested in 1988 that endophytes play a role in the defense systems of trees. Because life cycles of endophytes are considered to be much shorter than the life cycle of their host, they may evolve faster in their host, resulting in higher selection of antagonistic forms that contribute to resistance against short-living pathogens and herbivores. Later, in 1991, Carroll suggested that endophyte-mediated induced resistance occurs in Douglas fir trees (146). Endophytes may induce plant defense reactions, so-called induced systemic resistance (ISR), leading to a higher tolerance of pathogens (147, 148). There is increasing evidence that at an initial stage, interactions between beneficial microorganisms and plants trigger an immune response in plants similar to that against pathogens but that, later on, mutualists escape host defense responses and are able to successfully colonize plants (148). Bacterial strains of the genera *Pseudomonas* and *Bacillus* can be considered the most common groups inducing ISR (reviewed in references 149 and 150), although ISR induction is not exclusive to these groups (151, 152). Bacterial factors responsible for ISR induction were identified to include flagella, antibiotics, *N*-acyl-homoserine lactones, salicylic acid, jasmonic acid, siderophores, volatiles (e.g., acetoin), and lipopolysaccharides (152, 153) (Fig. 2). The shoot endophyte *Methylobacterium* sp. strain IMBG290 was shown to induce resistance against the pathogen *Pectobacterium atrosepticum* in potato, in an inoculum-density-dependent manner (151). The observed resistance was accompanied by changes in the structure of the innate endophytic community. Endophytic community changes were shown to correlate with disease resistance, indicating that the endophytic community as a whole, or just fractions thereof, can play a role in disease suppression (151). In contrast to bacterial endophytes, fungal endophytes have less frequently been reported to be involved in protection of their hosts via ISR (154–156).

Fungal endophytes are better known for their capacity to produce compounds that have growth-inhibitory activities toward plant pathogens and herbivores. These compounds comprise alkaloids, steroids, terpenoids, peptides, polyketones, flavonoids, quinols, phenols, and chlorinated compounds (157–159) (Fig. 2). Alkaloids produced by the clavicipitaceous fungi of grasses are among the best-described compounds produced by endophytes. For example, the neurotoxic indole-diterpenoid alkaloids, so-called lolitrems, are responsible for intoxication of cattle grazing on the endophyte-infected grass (160, 161). Some of these compounds, as well as some other alkaloids, are important for protection of the plant against insect herbivores (162, 163). Also, several reports have been published on the production of antiviral, antibacterial, antifungal, and insecticidal compounds by fungal endophytes, and most of these endophytes are transmitted horizontally, forming local infections in their hosts (157, 164). Not all horizontally transmitted fungal endophytes produce protective compounds, and due to the often small window of opportunity for

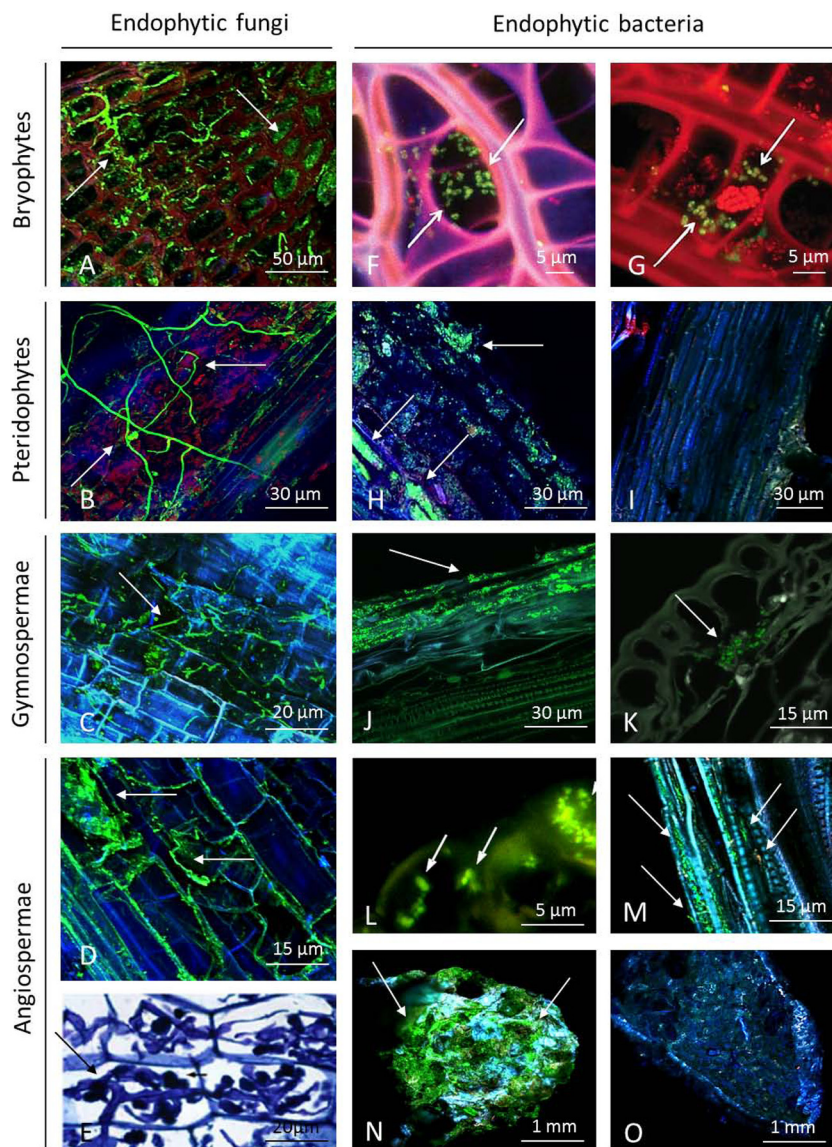


FIG 1 Microphotographs of endophytes showing (arrows) endophytic fungi in *Sphagnum* sp. (Alex Fluor 488-wheat germ agglutinin [WGA]) (A), endophytic fungi in a fern stem (Alex Fluor 488-WGA) (B), endophytic fungi in a stem of a *Pinus* sp. (Alex Fluor 488-WGA) (C), fungal endophytes in a stolon of a *Trifolium* sp. (Alex Fluor 488-WGA) (D), and mycorrhiza colonizing *Eleutherococcus sieboldianus* (toluidine blue) (E). (F and G) Bacterial endophytes in *Sphagnum magellanicum* (fluorescence *in situ* hybridization [FISH] with probes targeting *Alphaproteobacteria* [F] and *Planctomycetes* [G]). (H and I) Bacterial endophytes in fern leaves (double labeling of oligonucleotide probes-fluorescence *in situ* hybridization [DOPE-FISH] with EUBMIX-FLUOS probe for all bacteria [H] and with NONEUB-FLUOS probe [I]). (J and K) Colonization of Scots pine seedling by green fluorescent protein-tagged *Methylobacterium extorquens* DSM13060. (L) Bacterial endophytes in flowers of grapevine plants (FISH with EUBMIX-Dylight488 and LGC-Dylight549 probes, targeting all bacteria and *Firmicutes*, respectively). (M) Bacterial endophytes in the xylem of grapevine plants (DOPE-FISH with EUBMIX-FLUOS and HGC69a-Cy5 probes, targeting all bacteria and *Actinomyces*, respectively). (N and O) Bacterial endophytes in a nodule of *Medicago lupulina* (DOPE-FISH with EUBMIX-FLUOS probe targeting all bacteria [N] and with NONEUB-FLUOS probe [O]). (Panel E reprinted from reference 362. Panels F and G reprinted from reference 17 by permission from Macmillan Publishers Ltd. [copyright 2011]. Panels J and K reprinted from reference 369 with kind permission from Springer Science and Business Media. Panel L reprinted from reference 18 with kind permission from Springer Science and Business Media. Panel M reprinted from reference 363 by permission of the Society for Molecular Biology and Evolution.) All photographs show environmental samples, except those in panels J and K. Note that Alexa Fluor 488-WGA can also detect microbes other than fungi.

contact with plant pathogens, in both time and space, their role in host protection against plant pathogens is still under dispute. A study made with cacao plants indicated that pathogens commonly colonize tree leaves but that infection does not always result in the occurrence of disease, and even that they can act as beneficial or harmless endophytes in their host (165–167). A recent report supported this finding and further demonstrated that production of

endophytic antimicrobial compounds by endophytes can be induced by the presence of a pathogen (168).

Bacterial endophytes also produce antimicrobial compounds (Fig. 2). For example, the endophyte *Enterobacter* sp. strain 638 produces antibiotic substances, including 2-phenylethanol and 4-hydroxybenzoate (169). Generally, endophytic actinomycetes are the best-known examples of antimicrobial compound produc-

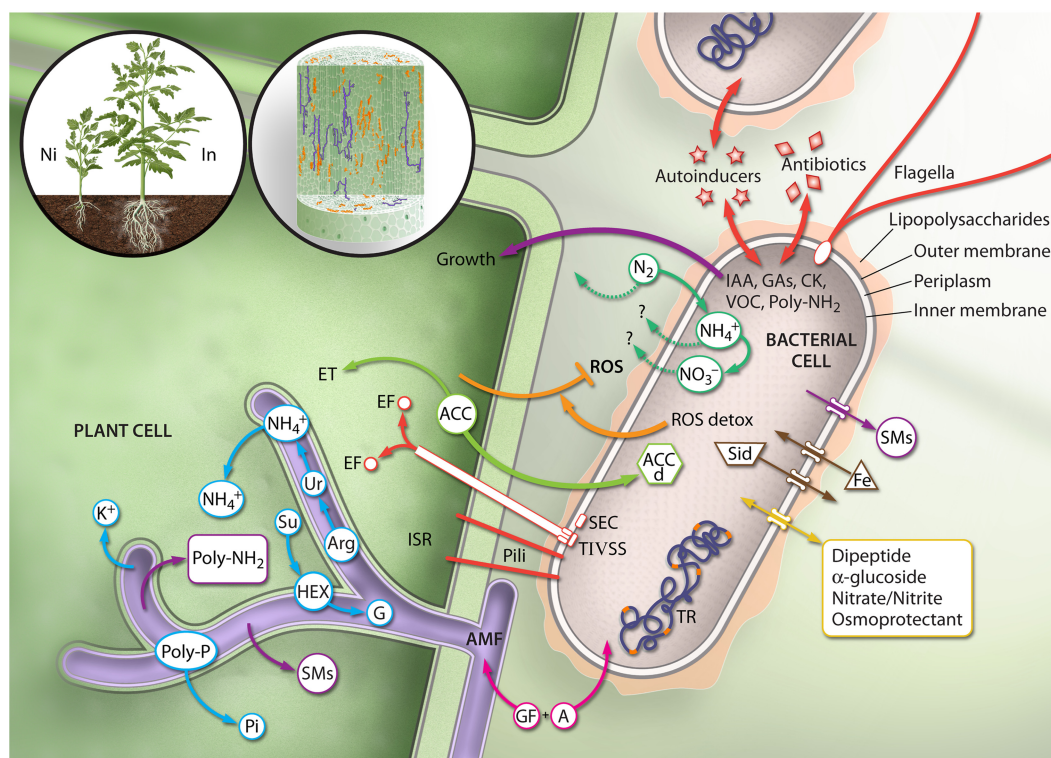


FIG 2 Beneficial properties of endophytes. The left panel shows plants inoculated (In) with beneficial microorganisms that significantly improve plant growth compared to noninoculated (Ni) plants. Various microorganisms, in particular bacteria (orange) and fungi (purple), can colonize the internal tissues of the plant (middle panel). Once inside the plant, the endophytic bacteria and fungi interact intimately with the plant cells and with surrounding microorganisms (large panel). Endophytic fungi, represented here as arbuscular mycorrhizal fungi (AMF) (lilac), might form specialized structures, called arbuscules, where plant-derived carbon sources, mainly sucrose (Su), are exchanged for fungus-provided phosphate (Pi), nitrogen (NH_4^+), and potassium (K^+) elements (blue). Plant cytoplasmic sucrose is transported to the periarbuscular space, where it is converted to hexose (HEX) to be assimilated by the fungus. Hexose is finally converted to glycogen (G) for long-distance transport. Phosphate and nitrogen are transported inside the fungal cytoplasm as polyphosphate granules (Poly-P), which are converted to Pi and arginine (Arg) in the arbuscule. Pi is transported to the host cytoplasm, whereas Arg is initially converted to urea (Ur) and then to ammonium (NH_4^+). Fungal and bacterial plant hormones, such as auxins (IAA), gibberellins (GAs), cytokinins (CKs), volatile organic compounds (VOCs), and polyamines (Poly- NH_2), as well as secondary metabolites (SMs), are transferred to the host (violet). Various bacterial structures, such as flagella, pili, secretion system machineries (e.g., TIV SS and SEC), and lipopolysaccharides, as well as bacterium-derived proteins and molecules, such as effectors (EF), autoinducers, and antibiotics, are detected by the host cells and trigger the induced systemic resistance (ISR) response (red). ACC, the direct precursor of ethylene (ET), is metabolized by bacteria via the enzyme ACC deaminase (ACCd), thus ameliorating abiotic stress (light green). A range of reactive oxygen species detoxification (ROS detox) enzymes might also ameliorate the plant-induced stress (orange). Diazotrophic bacterial endophytes are capable of fixing atmospheric nitrogen (N_2) and might actively transport NH_4^+ and nitrate (NO_3^-) to the host (dark green). Bacterial processes of siderophore production (Sid) and uptake (Fe) that are involved in plant growth promotion, biocontrol, and phytoremediation are shown in brown. Examples of various substrates on which the transmembrane proteins are enriched among endophytes are shown in yellow. Transcriptional regulators (TR) are also shown (orange). Communications and interactions between cells of microorganisms dwelling inside the plant tissues are promoted by growth factor (GF), antibiotic (A) (fuchsia), and autoinducer molecules.

ers, and compounds discovered so far include munumbicins (170), kakadumycins (171), and coronamycin (172). Recently, multicyclic indolosesquiterpenes with antibacterial activity were identified in the endophyte *Streptomyces* sp. HKI0595, isolated from the mangrove tree (*Kandelia candel*) (173), and spoxazomicins A to C, with antitrypanosomal activity, were found to be produced by *Streptosporangium oxazolinicum* strain K07-0450^T, isolated from orchid plants (174). Some of these compounds appear to be valuable for clinical or agricultural purposes (175), but their exact roles in plant-microbe interactions still need to be elucidated.

Production of additional secondary metabolites. Secondary metabolites are biologically active compounds that are an important source of anticancer, antioxidant, antidiabetic, immunosuppressive, antifungal, anti-oomycete, antibacterial, insecticidal, nematocidal, and antiviral agents (157, 175–182). In addition, endophytes produce secondary metabolites that are involved in

mechanisms of signaling, defense, and genetic regulation of the establishment of symbiosis (183). Besides the production of secondary metabolite compounds, endophytes are also able to influence the secondary metabolism of their plant host (182). This was demonstrated in strawberry plants inoculated with a *Methylobacterium* species strain, in which the inoculant strain influenced the biosynthesis of flavor compounds, such as furanones, in the host plants (184–186). Recently, bacterial endophytes, along with bacterial methanol dehydrogenase transcripts, were localized in the vascular tissues of strawberry receptacles and in the cells of achenes, the locations where the furanone biosynthesis gene is expressed in the plant (187). Similarly, biosynthesis and accumulation of phenolic acids, flavan-3-ols, and oligomeric proanthocyanidins in bilberry (*Vaccinium myrtillus* L.) plants were enhanced upon interaction with a fungal endophyte, a *Paraphaeosphaeria* sp. strain (188).

Iron homeostasis. Some bacterial and fungal endophytes are

producers of vivid siderophores (153, 189–192). Siderophores are essential compounds for iron acquisition by soil microorganisms (193, 194), but they also play important roles in pathogen–host interactions in animals (195, 196). The role of siderophores produced by endophytes in plant colonization is unknown, but it has been suggested that these compounds play a role in induction of ISR (153) (Fig. 2). Furthermore, siderophore production was shown to play an important role in the symbiosis of *Epichloë festucae* with ryegrass, as shown upon interruption of the siderophore biosynthesis gene cluster in *E. festucae* (191). It is possible that siderophores modulate iron homeostasis in *E. festucae*-infected ryegrass plants. Siderophores produced by endophytic *Methylobacterium* strains are also involved in suppression of *Xylella fastidiosa*, the causative agent of citrus variegated chlorosis in *Citrus* trees (189). A recent comparative genomic analysis of proteobacterial endophytes revealed that strains lacking the gene clusters involved in siderophore biosynthesis have a larger total number of genes encoding membrane receptors for uptake of Fe^{3+} -siderophore complexes, hence potentially allowing them to take up siderophores produced by other endophytes (197).

Protection against biotic and abiotic stresses. Whereas most of the described endophytes protect the plant from biotic stresses, some endophytes can also protect the plant against different abiotic stresses. For example, fungal strains of *Neotyphodium* spp. were shown to be able to increase tolerance toward drought in grass plants by means of osmo- and stomatal regulation (198), and they protected the plants against nitrogen starvation and water stress (199). The root fungal endophyte *Piriformospora indica* was shown to induce salt tolerance in barley (200) and drought tolerance in Chinese cabbage plants (201). In both cases, increases in antioxidant levels were the proposed mechanisms behind elevation in stress tolerance in these plants. Colonization of fungal endophytes of the genus *Trichoderma* in cacao seedlings also resulted in a delay in the response to drought stress (202), and the bacterial endophyte *Burkholderia phytofirmans* strain PsJN elevates drought tolerance levels in maize (203) and wheat plants (204). Furthermore, fungal endophytes have been shown to interfere with cold tolerance of rice plants (205), and *B. phytofirmans* strain PsJN has been shown to enhance chilling tolerance in grapevine plantlets (206).

ACC deaminase is a bacterial enzyme that is often associated with alleviation of plant stress (Fig. 2). This enzyme is responsible for lowering the levels of ethylene in the plant by cleaving the plant-produced ethylene precursor 1-aminocyclopropane-1-carboxylate (ACC) to ammonia and 2-oxobutanoate, preventing ethylene signaling (207). The plant hormone ethylene acts in the germination of seeds and in response to various stresses, and it is the key regulator of colonization of plant tissue by bacteria (208). This suggests that, apart from stress alleviation, ACC deaminase supports colonization of a number of bacterial endophytes. When the ACC deaminase gene of *B. phytofirmans* PsJN was inactivated, the endophyte lost the ability to promote root elongation in canola seedlings (209). Another study performed on cut flowers indicated that bacterial endophytes are able to colonize the shoot and that ACC deaminase delays flower senescence (210).

Plant growth stimulation. Some endophytes are involved in plant growth promotion, despite the fact that they are promoting growth at the expense of obtaining valuable nutrients provided by the host plant (211–213). High endophyte infection loads in plants indicate that benefit–cost balances are at least neutral or

positive, suggesting that most endophytes must be beneficial to their hosts. Such beneficial effects may result from interference in photosynthesis and carbon fixation processes taking place in plants. A fungal grass endophyte strain of *Neotyphodium lolii* was found to influence CO_2 fixation but was not shown to be able to interfere with light interception, photochemistry, or net photosynthesis (214). No effect on photosynthesis, stomatal conductance, photosynthetic water use efficiency, or the maximum and operating efficiencies of photosystem II was found in poplar trees inoculated with the bacterial plant growth-promoting endophyte *Enterobacter* sp. 638 (215). On the other hand, inoculation of wheat with the bacterium *B. phytofirmans* strain PsJN increased the photosynthetic rate, CO_2 assimilation, chlorophyll content, and water use efficiency under drought conditions (204).

Phytohormone production by endophytes is probably the best-studied mechanism of plant growth promotion, leading to morphological and architectural changes in plant hosts (213, 216, 217). The ability to produce auxins and gibberellins is a typical trait for root-associated endophytes (213, 216–219). It was proposed that indole-3-acetic acid (IAA), a member of the auxin class, increases colonization efficiency (220), possibly via interference with the host defense system (221), and production of this compound or related compounds may be an important property for plant colonization by endophytes (Fig. 2). Cytokinin production is commonly observed in endophytes, but on one occasion, in a root-colonizing fungal strain of *Piriformospora indica*, cytokinin biosynthesis was demonstrated and mutational deletions in cytokinin biosynthesis genes resulted in abortion of any plant growth-promoting effect (222).

Besides the production of plant growth hormones, additional mechanisms for plant growth promotion exist. Adenine and adenine ribosides have been identified as growth-promoting compounds in endophytes of Scots pine (223). Volatile compounds, such as acetoin and 2,3-butanediol, can stimulate plant growth (224–226) and are produced by some bacterial endophytes (227, 228). Polyamines affect plant growth and development in plant–mycorrhiza interactions (229) and are produced by the bacterium *Azospirillum brasilense* (230). It can be expected that additional, not yet understood mechanisms exist among plant-associated bacteria to promote plant growth.

Nitrogen fixation. Nutrient acquisition for plants via nitrogen fixation is another mechanism behind plant growth promotion. This trait is well studied in rhizobial and actinorhizal plant symbioses. Several root endophytes fix nitrogen (e.g., *Acetobacter diazotrophicus*, *Herbaspirillum* spp., and *Azoarcus* spp.) (231, 232), but the efficiencies of nitrogen fixation in free-living endophytes are far lower than those in root nodules of leguminous plant–rhizobium interactions (233). One exception is the relatively high nitrogen fixation efficiency observed in endophytic strains of *Gluconacetobacter diazotrophicus* in symbiosis with sugarcane plants (234). Other *G. diazotrophicus* strains were shown to be present in the microbiome of pine needles, including some potential N_2 -fixing strains (235). This indicates that *G. diazotrophicus* strains play important roles as nitrogen fixers in wider taxonomic ranges of host plants. Another example of a N_2 -fixing endophyte is *Paenibacillus* strain P22, which has been found in poplar trees (13). Strain P22 contributed to the total nitrogen pool of the host plant and induced metabolic changes in the plant. Nitrogen fixation contributes to the fitness of the host plant, especially in nitrogen-poor environments. Even if the quantities of fixed nitrogen mea-

sured in single nitrogen-fixing species are low, it remains to be clarified if the fixed N is for the endophytes' own demands and/or for provision to the host plant (236).

In summary, various mechanisms in endophytes can explain the profound effects that endophytes have on their plant hosts. A recent report indicates that endophyte infection can also affect the gender selection of the host plant (237), which suggests that many new properties remain to be identified among endophytes.

Plant-Microbe Symbioses Leading to Improved Plant Fitness

Endophytes taxonomically differing from AMF and rhizobia were also shown to confer increased fitness to their hosts (238, 239). As an example, spotted knapweed (*Centaurea stoebe*) became more competitive toward bunchgrass (*Koeleria macrantha*) upon inoculation with the fungal endophyte *Alternaria alternata* (238). Stimulation of the production of secondary compounds by the endophyte played an important role in increased fitness of the host plant. However, inoculation with other *Alternaria* sp. endophytes did not result in increased fitness of knapweed plants (239), indicating that the endophyte-host plant interaction was strain specific. In another case, it was shown that infection of wild red fescue plants with the ergot fungus *Claviceps purpurea*, a seed pathogen in many grass species, resulted in decreased herbivory by sheep (240). In association with its host, *C. purpurea* produces alkaloids that are toxic to mammalian species, thus protecting the host from predation. From this case, it is clear that particular microorganisms or taxa showing a lifestyle typical for endophytes can be both pathogenic and beneficial for their host. It was furthermore shown that plant-endophyte interactions can shift the gender balance in the offspring of the plant host. The fungus *Epichloe elymi*, an endophyte in *Elymus virginicus* plants, is vertically and maternally transmitted from parent to offspring plants, thereby increasing its opportunity to establish new infections in succeeding plant generations (237). Manipulation of the sex ratio in offspring is an example of how endophytes can manipulate the fitness of their hosts, in analogy to *Wolbachia* infection of particular insect species, indicating that manipulation of the gender balance in offspring is common among higher eukaryote-microbe interactions (241).

DECIPHERING THE BEHAVIOR OF ENDOPHYTES BY COMPARATIVE GENOMIC ANALYSIS

Comparative genomics is an important tool for identifying genes and regulons that are important for plant penetration and colonization by endophytes (242). Specific properties discriminating endophytes from closely related nonendophytic strains have been found on several occasions (169, 197, 243–246). Lateral gene transfer (e.g., by mobile elements, such as plasmids and genomic islands) plays an important role in the acquisition of properties responsible for the capacity of bacteria and fungi to colonize the endosphere of plants. As an example, the assembled genome of the obligate biotroph fungus *Rhizophagus irregularis* was shown to contain up to 11% transposable elements (244). No loss of metabolic complexity was detected, only a drift of genes involved in toxin synthesis and in degradation of the plant cell wall. Also, the genome sequence of the competent bacterial endophyte *Enterobacter* sp. 638 revealed many transposable elements, which were often flanked by genes relevant to host-bacterium interactions (e.g., amino acid/iron transport, hemolysin, and hemagglutinin

genes), as well as a large conjugative plasmid important for host colonization (169).

A comparative genomic and metabolic network study revealed major differences between pathogenic ($n = 36$) and mutualistic ($n = 28$) symbionts of plants in their metabolic capabilities and cellular processes (246). Genes involved in biosynthetic processes and functions were enriched and more diverse among plant mutualists, while genes involved in degradation and host invasion were predominantly detected among phytopathogens. Pathogens seem to require more compounds from the plant cell wall, whereas plant mutualists metabolize more plant-stress-related compounds, thus potentially helping in stress amelioration. The study revealed the presence of secretion systems in pathogen genomes, probably needed to invade the host plants, while genomic loci encoding nitrogen fixation proteins and ribulose biphosphate carboxylase/oxygenase (RubisCO) proteins were more exclusive to mutualistic bacteria (246). Bacteria carrying relatively large genomes are often able to successfully colonize a wide range of unrelated plant hosts, as well as soils, whereas strains with smaller genomes seem to have a smaller host range (247).

Comparative Genomics To Elucidate Specific Properties That Evolved in Bacterial Endophytes

To further expand on potential functional and mechanistic aspects of endophytes, we compared the genomes of 40 well-described bacterial strains which were isolated from the plant endosphere (i.e., endophytes) with those of 42 nodule-forming symbionts, 29 well-described plant bacterial pathogens, 42 strains frequently found in the rhizosphere (i.e., rhizosphere bacteria), and 49 soil bacteria (see Data Set S4 in the supplemental material). Sequences from protein-encoding genes of each genome were assigned KEGG Ortholog (KO) tags by using the Integrated Microbial Genome (IMG) comparative analysis system (248). A feature-by-sample contingency table was created, using properties with abundances of $>25\%$ and samples within each group with $<98\%$ functional similarity. The assigned KO tags were normalized by cumulative sum scaling (CSS) normalization, and then a mixture model that implements a zero-inflated Gaussian distribution was computed to detect differentially abundant properties by using the metagenomeSeq package (249). A comparison of relevant properties in the process of host colonization and establishment for each investigated group (i.e., nodule-forming symbionts, phytopathogens, and bacterial strains isolated from the rhizosphere and from soil) and for endophytes is shown in Table 3. We are aware of the fact that endophytes may colonize the rhizosphere (soil) or may even, under certain circumstances, have a phytopathogenic lifestyle (as discussed in other parts of this review). However, the aim of the comparative genomic analysis was to obtain indications of potential typical endophytic properties, which require further confirmation.

Motility and chemotaxis. The ability to sense and respond to environmental cues is one of the major properties driving colonization of microorganisms (249–252). Our comparative genomic analysis of properties involved in chemotaxis and motility of bacteria suggested that protein-encoding genes related to the use of aspartate/maltose (Tar) and dipeptides (Tap) are more abundant among endophytes than among strains obtained from the rhizosphere. The response regulator proteins CheBR and CheC and the flagellum biosynthesis and motility mechanisms are more abundant among endophytes than among phytopathogens (Table 3).

TABLE 3 Comparative genomics of properties relevant to plant colonization and establishment^a

Category and feature (gene)	Log ₂ fold change in abundance in the indicated group versus endophytes			
	Symbionts	Phytopathogens	Rhizosphere bacteria	Soil bacteria
Chemotaxis and motility				
Aerotaxis (<i>aer</i>)	−0.983***	0.029	−0.259	−0.354
Serine chemotaxis (<i>tsr</i>)	−0.697**	0.471*	−0.284	0.162
Aspartate/maltose chemotaxis (<i>tar</i>)	−0.315	−0.262	−0.276*	−0.041
Ribose chemotaxis (<i>rbsB</i>)	1.076***	−0.423	−0.108	−0.252
Galactose chemotaxis (<i>mgIB</i>)	−0.257***	0.030	0.390***	0.283**
Dipeptide chemotaxis (<i>tap</i>)	−0.174**	−0.172	−0.215***	−0.089
Response regulators (<i>cheBR</i>)	−0.276	−0.519***	−0.153	−0.280*
Response regulator (<i>cheV</i>)	−0.880***	−0.271	0.143	0.069
Response regulator (<i>cheD</i>)	−0.206*	−0.086	0.040	0.009
Response regulator (<i>cheC</i>)	−0.367*	−0.861***	0.096	−0.298
Response regulator (<i>cheZ</i>)	−0.271	−0.202	−0.396***	−0.155
Flagellar apparatus (<i>fliI</i>)	−0.252**	−0.201*	−0.149	0.045
Chemotaxis and motility (<i>motA</i>)	−0.555***	−0.297*	0.094	−0.065
Signal transduction—two-component systems				
Magnesium assimilation (<i>phoQ-phoP</i>)	−0.951***	0.052	−0.034	0.042
Stress (<i>rstB-rstA</i>)	−0.951***	−0.022	−0.005	0.070
Carbon source utilization (<i>creC-creB</i>)	−0.726***	0.077	−0.098	−0.016
Multidrug resistance (<i>baeS-baeR</i>)	−0.804***	0.032	0.074	0.000
Copper efflux (<i>cusS-cusR</i>)	−0.821***	−0.415	0.258	0.300
Carbon storage regulator (<i>barA-uvrY</i>)	−0.989***	−0.044	−0.058	0.017
Antibiotic resistance (<i>evgS-evgA</i>)	−0.868***	−0.522***	0.143	−0.288
Nitrogen fixation/metabolism (<i>ntrY-ntrX</i>)	−0.037	−0.233***	−0.615***	−0.089
Type IV fimbria synthesis (<i>pilS-pilR</i>)	−0.902***	0.038	0.039	0.180
Amino sugar metabolism (<i>glrK-glR</i>)	−0.974***	−0.021	−0.061	0.232
Twitching motility (<i>chpA-chpB</i>)	−0.783***	0.120	0.026	0.003
Extracellular polysaccharide (<i>wspE-wspR</i>)	−0.612***	−0.072	0.044	−0.023
Cell fate control (<i>pleC-pleD</i>)	−0.131***	−0.255**	−0.639***	0.094
Redox response (<i>regB-regA</i>)	−0.004	−0.204*	−0.099	−0.136
Transcriptional regulators				
Nitrogen assimilation (<i>nifA</i>)	−0.133	−0.757***	−0.359***	−0.220
Carbon storage regulator (<i>sdiA</i>)	0.617***	−0.067	−0.055	−0.279*
Biofilm formation (<i>crp</i>)	−0.976***	0.036	−0.036	0.068
Nitric oxide reductase (<i>norR</i>)	−0.625***	−0.156*	0.193	0.129
NAD biosynthesis (<i>nadR</i>)	−0.257***	0.012	−0.103	−0.079
Beta-lactamase resistance (<i>ampR</i>)	0.091	0.016	−0.060	−0.339***
Pyrimidine metabolism (<i>pyrR</i>)	−0.326**	−0.051	0.121	0.015
Thiamine metabolism (<i>tenA</i>)	0.070	−0.976***	0.109	0.195
Stress-related enzymes				
Glutathione peroxidase (<i>btuE</i>)	−0.360**	−0.031	0.104	−0.195
Glutathione S-transferase (<i>gst</i>)	0.562**	−0.435*	−0.230	−0.351
Catalase (<i>katE</i>)	−0.362*	−0.237	0.084	0.042
Transport system				
ABC, capsular polysaccharide (<i>kpsT</i>)	−0.045	−0.277***	−0.244*	−0.221
ABC, thiamine-derived products (<i>thiY</i>)	−0.449**	−0.958***	0.000	0.000
ABC, spermidine/putrescine (<i>potD</i>)	0.718***	−0.308**	0.092	0.081
ABC, dipeptide (<i>dppF</i>)	0.204**	−0.230***	−0.027	0.09
ABC, branched-chain amino acid (<i>livK</i>)	0.571	−0.884**	−0.629	−0.734
ABC, cystine (<i>fliY</i>)	−0.28	−0.270*	0.225	−0.355*
ABC, methionine (<i>metN</i>)	−0.478***	−0.336*	0.031	−0.163
ABC, histidine (<i>hisJ</i>)	−0.302	−0.096	0.349*	−0.266*
ABC, lysine/arginine/ornithine (<i>argT</i>)	0.216	−0.336	0.464	−0.182
ABC, L-arabinose (<i>araG</i>)	0.145	−0.067	0.066	−0.342***
ABC, rhamnose (<i>rhaT</i>)	−0.129	−0.826***	−0.043	−0.724***
PTS, cellobiose (<i>celB</i>)	−1.425***	−0.947***	−0.073	−0.146
PTS, glucose (<i>ptsG</i>)	−0.860***	0.000	0.000	0.000
PTS, mannose (<i>manY</i>)	−0.433***	−0.287**	−0.374***	−0.264*

(Continued on following page)

TABLE 3 (Continued)

Category and feature (gene)	Log ₂ fold change in abundance in the indicated group versus endophytes			
	Symbionts	Phytopathogens	Rhizosphere bacteria	Soil bacteria
PTS, ascorbate (<i>sgaA</i>)	−0.433**	0.003	−0.207	0.158
PTS, phosphocarrier (<i>furB</i>)	−0.317*	−0.007	−0.065	0.059
Others, multidrug (<i>mdtB</i>)	0.076	−0.042	−0.217**	0.134
Other, tricarboxylic (<i>tctA</i>)	0.670***	−0.018	0.352*	0.481*
Others, C ₄ -dicarboxylate (<i>dctP</i>)	−0.123	−0.462*	0.382*	0.553**
Others, membrane pore protein (<i>ompC</i>)	−1.149***	0.090	−0.053	0.071
Secretion systems				
Type I RaxAB-RaxC system (<i>raxB</i>)	−0.270	0.357	−0.234	−0.186
Type II general pathway protein (<i>gspD</i>)	−0.199	0.213	−0.265	0.064
Type III secretion core apparatus (<i>ycsJ</i>)	0.354*	0.263**	0.051	−0.181**
Type IV conjugal DNA protein (<i>virB2</i>)	0.370	0.125	−0.718***	−0.143
Type VI Imp/Vas core components (<i>hcp</i>)	−0.360	−0.038	−0.045	0.095
Twitching motility protein (<i>pilJ</i>)	−0.850***	0.058	0.028	−0.002
Type I pilus assembly protein (<i>fimA</i>)	−0.676***	−0.300	0.282	0.158
Plant growth-promoting properties				
Nitrogenase (<i>nifH</i>)	0.301**	−0.676***	0.226	0.030
ACC deaminase (<i>acdS</i>)	0.118	0.223	0.119	−0.344**
Acetoin reductase (<i>budC</i>)	0.024	−0.259***	−0.024	−0.059
Acetolactate decarboxylase (<i>alsD</i>)	−1.000***	0.000	0.000	0.000
Butanediol dehydrogenase (<i>butB</i>)	−0.089	−0.090	0.469**	−0.319
IAA biosynthesis, IAM pathway (<i>amiE</i>)	0.201	−0.067	−0.017	−0.029
IAA biosynthesis, IPyA pathway (<i>ipdC</i>)	0.077	−0.157	0.291***	−0.043
IAA biosynthesis, IAN pathway (<i>nir</i>)	−0.156	0.088	0.084	−0.019
IAA biosynthesis, IAN pathway (<i>nthAB</i>)	−0.136	−1.054***	−0.596***	−0.147

* The relative abundances of the assigned functional properties in each investigated group (symbionts [$n = 42$], phytopathogens [$n = 29$], rhizosphere bacteria [$n = 42$], or soil bacteria [$n = 49$]) compared to endophytes ($n = 40$) are shown as normalized log₂ fold changes. Negative values are shown if the endophyte group has a higher abundance. Significant changes were computed with a zero-inflated Gaussian mixture model, and the alpha levels, denoted by *, **, and ***, were assigned to q -value thresholds of 0.05, 0.01, and 0.001, respectively.

These results indicate the specificity of aspartate and dipeptide metabolism among endophytes, whereas serine metabolism seems to be used largely by phytopathogens. In addition, endophytes might be more responsive to different environmental cues than phytopathogens and nodule-forming symbionts.

Signal transduction. Regulation of two-component response systems is essential for the process of bacterial cell communication and fundamental for the synchronization of cooperative behavior (253, 254). In this category, bacterial endophytes differ mainly from nodule-forming symbionts and only marginally from the other investigated groups. Genes putatively involved in antibiotic resistance (*evgS* and *evgA*), redox response (*regB* and *regA*), nitrogen fixation and metabolism (*ntrY* and *ntrX*), and cell fate control (*pleC* and *pleD*) are found more prominently among endophytes than among phytopathogens and rhizobacteria (for the last two). A variety of energy-generating and energy-utilizing biological processes, including photosynthesis, carbon fixation, nitrogen fixation, hydrogen oxidation, denitrification, aerobic and anaerobic respiration, electron transport, and aerotaxis mechanisms, are known to be regulated in response to cellular redox balance (255) and might assist endophytes to thrive inside the host. The transmembrane nitrogen sensor protein NtrY interacts with the regulator protein NtrX to induce the expression of *nif* genes (256). Under nitrogen-limiting conditions, endophytes might be better able to fix nitrogen for their own benefit than phytopathogens or rhizobacteria. Overall, these results reveal distinct characteristics

that are suitable for bacteria to thrive and survive in different environmental niches and conditions.

Transcriptional regulators. Transcriptional regulators are essential for prokaryotes to rapidly respond to environmental changes, improving their adaptation plasticity, cellular homeostasis, and colonization of new niches (257). Genes putatively involved in the transcriptional regulation of nitrogen assimilation (*nifA*), reduction of nitric oxide (*norR*), regulation of carbon storage (*sdhA*), beta-lactamase resistance (*ampR*), pyrimidine metabolism (*pyrR*), and thiamine metabolism (*tenA*) are detected in significantly larger proportions among endophytes than among the other investigated groups (Table 3). Regulatory genes related to the stoichiometry of nitrogen and carbon metabolism and those involved in the metabolism of nucleotides and vitamins and in stress responses might be of great importance for a life inside plants. Nodule-forming symbionts and plant pathogens that also thrive inside plant tissues reveal mechanisms different from those in endophytes to cope with stress and metabolism of nutrients, suggesting that each group has its own regulatory set of genes required for its typical behavioral responses.

Detoxification and stress-related enzymes. Due to an abrupt burst of reactive oxygen species (ROS) and reactive nitrogen species (RNS), the internal compartments of plants are inhospitable niches for aerobic microorganisms. Therefore, enzymes with detoxification capacities are essential for plant endosphere colonization and may also function as ameliorating agents upon host-

induced stresses (258). Genes encoding glutathione peroxidase (*btuE*), glutathione S-transferase (*gst*), catalase (*katE*), and nitric oxide reductase (*norR*) are enriched, according to our analysis, in endophyte genomes compared to phytopathogen or nodule-forming symbiont genomes (Table 3). These ROS- and RNS-scavenging enzymes might assist endophytes to cope with the plant oxidative burst and might also ameliorate host biotic and abiotic stresses by protecting plant cells from oxidative damages (12, 259).

Transporters. Nutrient transport is an important function for life inside plants (169, 197). The proportion of endophytes harboring genes for ATP-binding cassette (ABC), major facilitator superfamily (MFS), phosphotransferase system (PTS), solute carrier family (SLC), and other transport systems varied largely in our analysis (Table 3). Genes putatively involved in the uptake of capsular polysaccharides, organic ions, peptides, amino acids, and carbohydrates were detected more prominently among endophytes than in the other investigated groups (Table 3). These results indicate the complexity of nutrient transport systems of endophytes, which might reflect their various lifestyle strategies for acquiring nutrients inside plants.

Secretion systems. Protein secretion plays an important role in plant-bacterium interactions (67, 260). Major differences in secretion systems of endophytes and nodule-forming symbionts were observed in our analysis (Table 3). Genes putatively involved in type III secretion systems are more typical of nodule-forming symbionts and phytopathogens than of endophytes, whereas they are detected in a significantly larger proportion of endophytes than soil bacteria (Table 3). This type of secretion system is more often employed by pathogens to manipulate host metabolism (261, 262). Conversely, type IV conjugal DNA-protein transfer secretion systems were detected more prominently among endophytes than among rhizosphere bacteria (Table 3). Type IV secretion is likely to be involved in host colonization and conjugation of DNA (263–265). Protein-encoding genes involved in adhesion to the host via twitching motility and type I pilus assembly are also detected more prominently among endophytes than among nodulating symbionts. These systems might be determinants of host colonization success (266, 267).

Genes involved in plant growth promotion. The nitrogenase (*nifH*) gene, putatively involved in the fixation of atmospheric N₂, was detected in a significantly larger proportion of endophytes than of phytopathogens (Table 3). Surprisingly, 28% of the investigated group of prokaryotic endophytes harbored this gene, indicating that it has an important function in improving plant productivity under conditions of N limitation (see above). One of the genes thought to be involved in plant stress alleviation, encoding 1-aminocyclopropane-1-carboxylate deaminase (*acdS*), is detected more prominently among endophytes than among soil bacteria. Recent analyses of bacterial endophyte genomes suggest that ACC deaminase is not as widely spread among endophytes as previously thought (197, 263). However, endophytes differ significantly in their favored pathways for the biosynthesis of the plant hormones acetoin, 2,3-butanediol, and IAA compared to phytopathogens or rhizosphere bacteria, thus suggesting some particular characteristics that promote plant growth.

To summarize, genomic differences can be found between the different functional groups (i.e., endophytes, nodule-forming symbionts, phytopathogens, rhizobacteria, and soil bacteria), but we have to be aware that borders between functional groups are

not clear-cut. Properties that are largely discriminative for endophytes compared to the other groups are a higher responsiveness to environmental cues, nitrogen fixation, and protection against reactive oxygen and nitrogen species. Endophytes might exhibit phytopathogenic effects under certain conditions, and rhizosphere bacteria might also be able to colonize plants internally. Furthermore, the balance between mutualism and antagonism depends on multiple parameters and might depend on a very fine-tuned interaction between microbial elicitors and plant responses (268).

PATHOGENS AND ENDOPHYTES: THE BALANCE OF THE INTERACTION IS CRUCIAL

Pathogenicity: Definition and Mechanisms

Pathogenicity to humans, animals, and plants is the most acclaimed feature of microorganisms. Traditionally, pathogens have been defined as causative agents of diseases, guided by Koch's postulates for more than a century and later advanced by making use of molecular markers (269). Next-generation sequencing-based technologies have drastically revolutionized our knowledge of the microbiome, and also of pathogens (270, 271). We learned particularly from the human microbiome that it is involved in many more diseases than recently thought and that pathogen outbreaks are associated with shifts of the whole community, including those supporting pathogens (272, 273). Recently, this was also shown for plant pathogens (140, 274).

The generally used definition of endophytes excludes pathogenic microorganisms *per se*. However, all recent studies have shown that plant-endophyte interactions have a much broader range reaching from beneficial to pathogenic (275, 276). Many potential human as well as plant pathogens have the capacity to colonize the plant endosphere (275, 277). Therefore, endophytes and internal pathogens share several mechanisms (277). Several studies have provided evidence that similar or even identical functions are responsible for beneficial interactions with plants and virulence in humans. For example, the involvement of siderophore uptake systems or extracellular enzymes is common to both beneficial bacteria and human pathogens (278). Dörr et al. (279) reported that type IV pili of the plant-associated *Azoarcus* sp. strain BH72 are responsible for adhesion to plant and fungal cells. Furthermore, the amino acid sequence of the pilus shows high similarities to those of the pili of human-associated strains of *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae*. While a mutant of *Pseudomonas fluorescens* deficient in a lauroyl transferase involved in lipid A biosynthesis resulted in impaired root colonization (280), a similar mutant of *Salmonella enterica* serovar Typhimurium was limited in its ability to colonize organs of the lymphatic system of mice (281). Type III secretion systems are responsible for the introduction of effectors into eukaryotic host cells, and they have been found in pathogenic bacteria as well as plant-associated bacteria with beneficial effects on host plants (282). Genome comparisons of plant- and human-associated *Stenotrophomonas* strains identified many similar properties responsible for host-microbe interactions (275), but also different ones, which included factors responsible for host invasion, antibiotic resistance, and several crucial virulence factors (283, 284). Interestingly, heat shock proteins were absent and a suicide vector activated at 37°C was identified in the plant-associated *Stenotrophomonas* strain (283). In addition, *Stenotropho-*

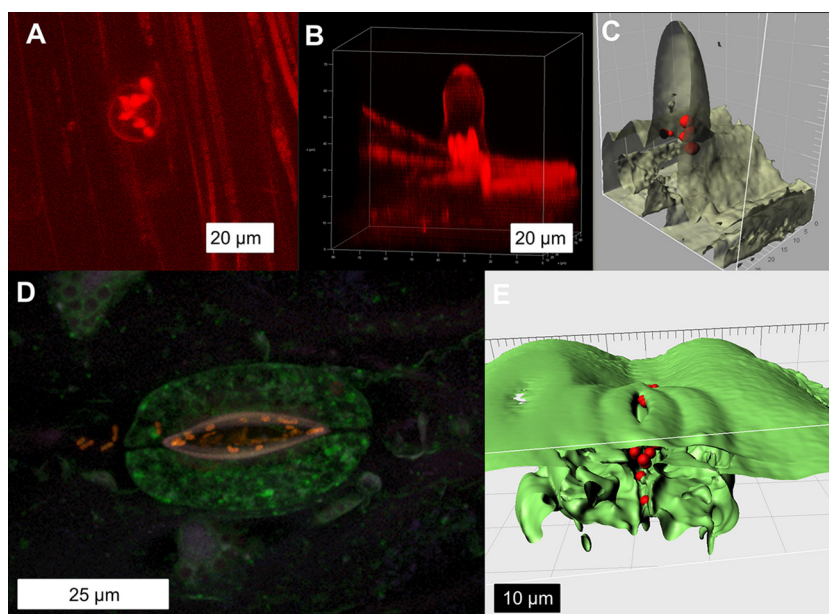


FIG 3 Colonization of endosphere tissues by clinical bacterial strains. Volume renderings are shown for confocal laser scanning micrographs for FISH analyses of stained *Stenotrophomonas maltophilia* cells (red signal) within the emerging lateral root of a tomato plant (beige signal) (A to C) and stained *Escherichia coli* cells (red signal) invading a lettuce leaf via a stoma (green signal) (D and E). (Panels A to C reprinted from reference 370 with kind permission from Springer Science and Business Media. Panel E reprinted from reference 371.)

omonas rhizophila DSM14405^T possessed unique genes for the synthesis and transport of the plant-protective compound spermidine, plant cell wall-degrading enzymes, and high salinity tolerance (283). The role of mutation frequency in niche adaptation was identified by Turrientes et al. (285). The factors described above are important mechanisms by which harmless bacteria can behave as pathogens with a change of host or host niche, upon which their virulence potential is frequently revealed to its full extent. *Stenotrophomonas maltophilia* is a multiresistant pathogen, and clinical and plant-associated strains show similar levels of resistance against clinically relevant antibiotics (286). For example, quinolone resistance mediated by the efflux pump SmeDEF is important for clinical issues but also for colonization of plant roots (287). In addition, clinical *Stenotrophomonas* strains are still able to colonize plant environments, such as tomato roots (Fig. 3A).

Occurrence of Potential Pathogens in the Endosphere of Plants

The plant endosphere can be colonized by plant, animal, and human pathogens. In plant microbiome analyses, several plant pathogens were identified, although no disease symptoms were observed (277). The fungal endophyte *Verticillium dahliae* is an interesting example; this is a pathogen which causes large yield losses in a broad range of crops, e.g., strawberry, potato, and olive (288). On the other hand, the fungus was found in many healthy plants as a commensal endophyte, e.g., in medicinal plants, potato, and grapevine (289). Moreover, “beneficial” strains of *V. dahliae* were used to biologically control *Ophiostoma novo-ulmi*, the fungus which causes Dutch elm disease (290). Animal and human pathogens, especially *Escherichia coli* pathovars (7, 242), are also able to colonize endospheres (291). Figure 3D shows the invasion of *E. coli* cells into lettuce leaves via stomata. Opportu-

nistic pathogens play a special role because plants, including the endosphere, are an important reservoir for emerging opportunistic pathogens (276, 277). There are many genera comprising endophytes, including *Burkholderia*, *Enterobacter*, *Herbaspirillum*, *Mycobacterium*, *Ochrobactrum*, *Pseudomonas*, *Ralstonia*, *Serratia*, *Staphylococcus*, *Stenotrophomonas*, and *Xylella*, that enter bivalent interactions with plant and human hosts. Several members of these genera show plant growth-promoting properties as well as excellent antagonistic properties against plant pathogens and have therefore been utilized to control pathogens or to promote plant growth (277). However, many strains of these species also successfully colonize human organs and tissues and thus cause diseases.

Enterobacteriaceae is a large family of Gram-negative bacteria that includes, along with many harmless symbionts, many of the more familiar, so-called enteric pathogens (292). Many members live in the intestines of animals, but interestingly, the plant endosphere is also a reservoir for enterobacteria (293, 294). In particular, the abundance of human enteric pathogens is enhanced after intermediate disturbances (274). Although the incidence of outbreaks of enteric pathogens associated with fresh produce in the form of raw or minimally processed vegetables and fruits has recently increased, the ecology of enteric pathogens outside their human and animal hosts is less well understood (7).

Which Functions Could Pathogens Have Inside Plants?

Plant microbiota, i.e., microbial communities associated with a particular plant, play an important role in plant growth and health. Microorganisms can support nutrient uptake and produce a broad range of phytohormones or influence the latter. Another important function is the involvement of plant-associated bacteria in pathogen defense (276). Resistance against leaf pathogens is often encoded in the plant genome but may also be mediated by plant-associated microorganisms (295). It is more difficult to find

resistance genes against soilborne pathogens. Cook et al. (296) suggested that antagonistic rhizobacteria fulfil this function.

Another hypothesis is that bacteria associated with the human diet, such as *Enterobacteriaceae*, act as stimuli for our immune systems. Recently, Hanski et al. (297) showed that declining environmental biodiversity is associated with reduced microbial diversity on human skin and enhanced allergic disposition, as shown through significant interactions with *Enterobacteriaceae*. Furthermore, they showed a positive association between the abundance of *Acinetobacter* organisms and interleukin-10 expression in peripheral blood mononuclear cells of healthy human individuals. Interleukin-10 is an anti-inflammatory cytokine and plays a central role in maintaining immune tolerance to harmless substances (298). The endotoxin derived from Gram-negative bacteria, such as *Enterobacteriaceae*, is known to have allergy-protective and immune-modulatory potentials (299). If plants are a natural reservoir of *Enterobacteriaceae*, then these bacteria must have been a “natural” part of our diet for a long time. Taking into account how many vegetables and fruits are eaten by people worldwide, these outbreaks seem to be more an accident than the norm, particularly considering that, traditionally, food was not processed and sterilized before being eaten. Therefore, the function of the plant-associated microbiome as an immune stimulant or “natural vaccination” was suggested by Berg et al. (300).

THE PLANT BIOME AND MULTIPARTITE INTERACTIONS

Our increasing understanding of the structure and complexity of microbial communities in various environments has led to comparisons between the microbiota associated with humans and those associated with plants, particularly with roots (301, 302). Plant roots have been suggested to be analogous to the human gut, as they are the primary organs interacting with the environment and mediating signal exchange and communication between plants and microorganisms. Microbiota of both animals and plants have important functions for host health by protecting against pathogens (247, 303) as well as regulating host gene expression and nutrient uptake and providing metabolic capacities (304). The plant microbiome can be considered an extension of the host phenotype (302, 305), and the plant secretory machinery has been suggested to play an important role in establishing an extended phenotype with microbial life (306).

Determinants of Endophyte Community Structures

The composition of endophyte communities is governed by biotic and abiotic factors. Most importantly, the plant, i.e., the host genotype and developmental stage, as well as the environment from which endophytes originate (such as soil for root endophytes and air for foliar fungal endophytes), contribute to community assembly; however, the magnitudes of the effects may differ between distinct systems. Few studies have attempted to evaluate the extents to which these parameters shape the endosphere microbiome. Rasche et al. (307) investigated potato-associated bacterial endophyte communities colonizing the lower stem sections of plants grown under greenhouse conditions. Different varieties, including genetically modified plants, were grown in contrasting soil types, and plants were sampled at different vegetation stages. In addition, the experiment included a pathogen (*Pectobacterium atrosepticum*) treatment. Molecular community analysis showed that the soil type was the most important driver of bacterial community composition, followed by the plant developmental stage.

Recently, a thorough investigation making use of next-generation sequencing technologies investigated root-associated microbiomes of eight diverse, inbred *Arabidopsis* accessions, cultivated in two different soil types (308). Although the developmental stage had less of an effect on structures of the microbial communities in that study, the effect of the soil environment was more pronounced than that of the plant genotype. Ding et al. (309) studied bacterial leaf endophyte communities associated with distantly related plant species grown under natural conditions. In their study, the host species was the main factor shaping the community composition, followed by sampling dates and sampling locations. Generally, genetically related plants seem to host more similar bacterial endophyte communities, although host effects have repeatedly been reported (8, 76, 307, 308, 310–313). Nevertheless, the host phylogenetic distance alone does not explain bacterial microbiota diversification (314). The host effect on bacterial communities can be explained by the fact that many or most bacterial endophytes enter the plants via roots. Different plant species and varieties are characterized by different root exudation patterns, which are likely to attract different microorganisms colonizing the rhizoplane and subsequently gaining entry into the plant. In addition, plant physiology and chemical or physical characteristics are likely to play a major role. This is evidenced by the finding of different bacterial communities in different plant tissues (315, 316).

Microbiota Associated with Plant Reproductive Organs

Seed transmission is well known for fungal endophytes. Recently, it was suggested that bacterial endophytes may also be transmitted via seeds. Johnston-Monje and Raizada (227) showed that seed endophyte diversity was conserved to a certain extent in maize seeds, from wild ancestors to modern varieties, across boundaries of evolution, ethnography, and ecology. Seed bacterial endophyte communities have been reported to be quite independent from the soil environment (317), suggesting that vertical transmission of bacterial endophytes might also contribute to the establishment and fitness of the host. The frequency of vertical transmission of bacterial endophytes along host generations is a matter of debate. Hardoim et al. (107) reported that up to 45% of the seed-borne bacterial community was transmitted vertically from two consecutive generations in rice plants. It is interesting that in insect-pollinated plants, such as apple plants, flower-associated bacterial communities were dominated by taxa that are rare in plants (318). This indicates that bacterial endophytes associated with reproductive organs of allogamous plants may have an origin different from that of bacterial endophytes associated with other organs and might derive from the air or from feeding insects. Some of these endophytes might be transmitted via seeds. The flowering and pollination properties of the host genotype likely influence the community composition of bacterial endophytes transmitted via seeds.

Grasses have very specific interactions with fungi, with many endophytes being transmitted vertically via host seeds, and communities are therefore greatly dependent on the host genotype (110, 319). Other fungal endophytes are transmitted via spores colonizing plant leaves or may derive from members of the soil environment colonizing roots (117, 285). Although the interaction between plant hosts and horizontally transmitted endophytes is less specific than the symbiosis between *Neotyphodium/Epichloë* and grasses, host genotype specificity has frequently been reported

for horizontally transmitted endophytes (320–323). Similarly to what has been described for bacterial endophytes, specific fungal communities colonize plant tissues representing distinct niches (324, 325). Above- and below-ground plant tissues seem to obtain their fungal endophytes from different sources. Root fungal endophytes are likely to derive from the soil environment (326), whereas fungal endophytes colonizing above-ground tissues are transmitted via spores in the air (327). Bacterial and fungal endophyte communities greatly differ between different plant developmental stages (307, 324), again indicating the tight interaction between endophytes and host physiology.

Multitrophic Interactions

The plant biome comprises the plant and multiple fungal and bacterial players, including both pathogens and mutualists, and is characterized by a dense network of multitrophic interactions, which are still poorly understood. Particularly in the case of tight interactions between the plant host and endophytes, signaling and recognition processes are highly important, inducing molecular, physiological, and morphological changes (328). However, plant-associated microorganisms may also influence plant pathways and phenotypes more generally. Quambusch et al. (329) reported distinct endophytic communities for easy- and difficult-to-propagate cherry genotypes, indicating the need for a specific microbiome, or at least specific microbiome components, for plant growth in general. The interaction of endophytes with their plant host may also affect its relationship with other microbes.

It is well known that endophytes may directly antagonize plant pathogens, which might be detectable in confrontation assays. Nevertheless, antimicrobial effects may also be induced by more sophisticated chemical communication. Combès et al. (168) demonstrated that *Paraconiothyrium variabile*, a fungal foliar (needle) endophyte, showed direct antagonism toward the phytopathogen *Fusarium oxysporum*; however, extracts of pure cultures did not show any effects. Only dual cultures of endophyte and pathogen led to competition-induced metabolite production. Oxylinins were identified as the induced metabolites, and their production was also associated with decreased mycotoxin production by the *Fusarium* pathogen. It is evident that chemical signaling and cross talk between endophytes and host plants are complex (330), and this example illustrates the importance of chemical communication not only between endophytes and plants but also between microorganisms. However, we are at the very beginning of understanding multitrophic metabolic interactions, which probably involve diverse chemical compounds produced by either the plant or microorganisms within the framework of their interaction (175, 183). Chemical interactions may also occur between fungal endophytes and endofungal bacteria. Hoffman and Arnold (331) reported that filamentous fungal endophytes frequently harbor diverse endohyphal bacteria, with mostly unknown importance. The same authors also recently found that such an endohyphal bacterium, a *Luteibacter* sp., greatly enhances IAA production from a foliar fungal endophyte, although the bacterium does not show IAA production when grown in pure culture under standard laboratory conditions (332). Another example of endofungal bacterial activity is toxin (rhizoxin) production by the fungus *Rhizopus microsporus*, which is responsible for rice seedling blight, but the actual toxin producer is the endofungal bacterium *Burkholderia endofungorum* (333, 334).

Bacteria might also play important roles in the interactions of

AMF with plants and may represent examples of the evolution of multipartner associations. Representatives of the *Mollicutes* and “*Candidatus* Glomeribacter,” a group of *Burkholderia*-related Gram-negative species, have been demonstrated to live in hyphae and spores of AMF (335, 336). Relationships of these so-called mycorrhiza helper bacteria with AMF are close, and these bacteria most likely contribute to colonization and formation of the mycorrhizal structures in plant roots (337, 338). Another example of tripartite interactions is provided by a virus-infected fungal endophyte of *Curvularia protuberata*, which systemically colonizes the geothermal grass *Dichanthelium lanuginosum* (119, 339, 340) and increases its tolerance to high temperatures. The host plant and the endophyte can tolerate temperatures only as high as 40°C when grown separately, but in symbiosis, the plant-fungus combination is able to grow at soil temperatures as high as 65°C.

Endophytes can be prone to phage infections, and in principle, phages infecting endophytes can modulate bacterial and fungal endophytic communities (339, 341, 342). Several studies indicate that phages can play important roles in microbial community structuring (343, 344). Phages infecting endophytes of horse chestnut were more virulent for endophytes of the same trees than those of other trees, indicating selective forces on endophytic communities and that their phages can be tree specific. These examples demonstrate that neither plants nor individual endophytes act independently but that multiple organisms interact and influence the performance of the plant (biome).

Interactions between Endophytes and Pathogens/Pests

Endophytes may increase the defense against herbivores, including insects that transmit pathogens (319, 345). Deterrence of herbivores is known to be mediated via *in planta* production of biologically active alkaloids in grasses by endophytes, which can reduce arthropod feeding and, consequently, damage to the host (346). However, in relation to wild grasses, Faeth and Saari (347) reported that herbivore abundance and species richness may be even greater on endophyte-infected plants with high alkaloid contents than on endophyte-free plants; they argued that herbivores may develop detoxification pathways. Endophyte infection in grasses has also been tested for reducing aphid-transmitted virus infections (348). Endophyte infection and alkaloid production resulted in reduced aphid feeding, as expected, but no effect on virus titers could be observed. Nevertheless, the impact of virus infection on the host was reduced in endophyte-infected plants, indicating that the endophyte induced a host response, which was probably responsible for this effect. The interactions between plants, endophytes, aphids, and viruses were also influenced by the host and endophyte genotypes (348) as well as by abiotic factors, such as temperature (349).

The endosphere microbiome composition is affected by pathogen infection (49, 350–353), potentially leading to effects on microbial functioning. Some studies reported a reduction of bacterial (351) and fungal (353) diversity in diseased or pathogen-containing plants. Douanla-Meli et al. (353) compared culturable fungal endophyte communities of healthy and yellowing citrus leaves. The latter showed higher levels of colonization by fungal endophytes but lower levels of richness than healthy leaves. *Phytoplasma* infection of grapevines resulted in a reduction in diversity of bacterial endophyte communities (351). On the other hand, Reiter et al. (49) found a higher diversity of bacterial potato endophytes due to the presence of *Pectobacterium atrosepticum*;

however, no disease symptoms were observed. Rasche et al. (307) reported that the extent to which *P. atrosepticum* affected the structure of bacterial endophytic communities depended on the plant genotype and on the soil environment. The various findings can be explained by the use of different plant hosts and pathogens and by the severity of disease. Pathogens induce a cascade of reactions leading to the synthesis of stress metabolites, including ROS or phytoalexins, and a range of stress signals, and these may provide a habitat with different physiological characteristics. Such an altered habitat is likely to support a differently structured endophyte community showing different functional characteristics. In addition, endophytes or rhizosphere bacteria that induce a systemic response in plants, such as *Methylobacterium* strains tested by Ardanov et al. (354), were reported to affect endophyte communities. The resulting bacterial community structures correlated with resistance or susceptibility to disease caused by *Pectobacterium atrosepticum*, *Phytophthora infestans*, and *Pseudomonas syringae* in potato and by *Gremmeniella abietina* in pine (354).

Interactions between Endophytes and Other Symbionts

In addition to the interactions between endophyte communities and phytopathogens, endophytes interact with other symbiotic microorganisms. Foliar fungal endophyte species composition was reported to be altered by AMF colonization (355). Wearn et al. (324) suggested that there is competition or antagonism between AMF and root endophytes, as they found negative correlations between mycorrhizal colonization and the presence of endophytes in roots of herbaceous grassland species. Some studies suggest that AMF colonization of grasses may be affected by the production of alkaloids or other allelopathic compounds by fungal endophytes (356–358). However, different AMF species or strains may behave/interact differently with plants and endophytes. For grasses, Larimer et al. (359) reported that *Glomus mossae* enhanced endophyte growth through increased tiller production, and in return, *G. mossae* showed higher colonization levels. On the other hand, colonization by another AMF species, *Glomus claroideum*, declined in endophyte-infected plants. In *Pinus sylvestris*, the interaction between a bacterial endophyte and an ectomycorrhizal fungus was shown to be species dependent, as endophytic *Methylobacterium extorquens* enhanced the growth of pine seedlings with one fungal species but decreased the growth when coinoculated with another ectomycorrhizal fungus (360).

In conclusion, the plant biome is characterized by multiple and complex interactions between the plant, the associated microbiota, i.e., endophytes with different functions, including pathogens, and the environment. The plant phenotype not only is determined by the response of the plant to the environment but also is regulated by the associated microbiota, the response of the microbiota to the environment, and the complex interactions between individual members.

CONCLUDING REMARKS

Technological developments, especially with respect to “-omics” technologies, will revolutionize our concepts on endosphere microbiomes. At present, we are better able to distinguish between properties specific to phytopathogens, endophytes, and other microorganisms from soil and plant habitats. This will allow us to better understand mutualists and pathogens, because from an ecological perspective, the boundaries between both groups are not always clear. Furthermore, microbial groups previously

thought to be distinctive of other environments, such as human pathogens in warm-blooded animals, have been demonstrated to thrive in plants. Genomics will teach us how microbial groups from other environments adapt to plant environments and will reveal the minimal genetic requirements for successful penetration and internal colonization of plants. Novel technologies will also allow us to investigate multiple interactions between microbial groups associated with plants and the plant host itself. Nowadays, we have a better capacity to analyze impacts of invading microorganisms on the whole endophytic community composition and functioning, and *vice versa*. We can also better explain the resilience of plants upon invasion by potentially deleterious microorganisms by the functioning and complexity of the endophytic communities. We must learn more, however, about the still unknown roles of endophytes, particularly the so-called commensal endophytes. This group, which causes no apparent effects on plant performance but lives on the metabolites produced by the host, is presumably the most dominant functional group among endophytes by quantity (2, 361). We expect to find hidden functions within this group and to learn more about the complexity of microbial interactions within plants, including the consequences for the host plant. We also need to learn more about the interactions between endophytes and plants as well as the mechanisms employed by all partners. It will be highly relevant to elucidate the physiological conditions present in endophytes and plants during colonization, as it can be expected that an endophyte will have different characteristics inside the plant compared to growth in the soil or in the lab. Similarly, research is needed to better understand under which conditions and by which mechanisms microorganisms exhibit harmful, beneficial, or neutral effects on plant performance. By implementing new technologies and multidisciplinary approaches, our understanding of endophyte biology and ecology will consistently evolve further, leading to a better knowledge of the plant holobiome.

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