

# Chapter 15

## Translating Endophyte Research to Applications: Prospects and Challenges

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**Abstract** The horizontally transmitted fungal endophytes cause symptomless infections of plants. Endophytes synthesize a diverse array of metabolites and enzymes, an attribute that reflects their milieu: the host plant and co-occurring microbes. We illustrate the versatility and utility of endophytes by highlighting examples of how they enhance plant tolerance to abiotic/biotic stressors, produce biomolecules with unique molecular architectures, and elaborate novel enzymes of industrial importance. After considering the challenges that have retarded the translation of these findings to payoffs, we suggest future directions, including the need to understand the ecology and *in planta* community structure of endophytes, to help fully realize their technological potential.

**Keywords** Fungal endophytes • Bioactive molecules • Stress tolerance • Abiotic stress • Biotic stress • Industrial enzymes • Lignocellulosic biomass

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## 15.1 Introduction

Horizontally transmitted fungal endophytes are asymptomatic endosymbionts of plants. Although endophytes represent a major community of plant-associated fungi, they have received much less attention compared to mycorrhiza (Porras-Alfaro and Bayman 2011; Parniske 2008). Though first defined as early as 1866 by de Bary, studies on endophytes intensified only during the last four decades motivated by a desire to identify undescribed species since these endosymbionts (especially those residing in tropical plants) had not been investigated. Results from initial morphological and molecular studies led to the notion of high endophyte diversity that mirrors the striking variety of plants in the tropics (Arnold et al. 2000; Hyde and Soyong 2008, but see Suryanarayanan et al. 2011). It is now established, however, that a core group of fungi consisting of species of *Colletotrichum*, *Pestalotiopsis*, *Phomopsis*, and *Xylaria* occur as endophytes in almost all tropical plants irrespective of their taxonomic affiliation or geographic location, and that endophyte diversity is not exceptionally high at least in the dry tropical regions (Suryanarayanan 2011). Such a wide host range of some endophytes could also be attributed to the production of select enzymes by the endophytes that help avoid recognition by the host plant's immune system (Cord-Landwehr et al. 2016) and to the accumulation of traits for survival under specific environmental conditions (Reddy et al. 2016). Furthermore, the broad ensemble of endophytes identified thus far has also gained attention due to their extraordinary synthetic capabilities.

Endophytes elaborate many novel secondary metabolites including those having antibacterial, -algal, -malarial, and -cancer properties (Suryanarayanan et al. 2009; Debbab et al. 2012; Kaushik et al. 2014; Wang et al. 2015a). In a few instances, an endophyte, in an axenic culture, even produces metabolites that are typically synthesized by its host in an axenic culture (Shweta et al. 2013a, b; Mohana Kumara et al. 2014). Endophytes are also a rich source of enzymes that have potential for use in production of various industrial products including pharmaceuticals (Govindarajulu et al. 2011; Nagarajan et al. 2014; Suryanarayanan et al. 2012) and biofuels (Govindarajulu et al. 2014; Thirunavukkarasu et al. 2015). These wide-ranging competencies may have evolved due to the multitrophic interactions of endophytes with the plant host and competition with other members of the plant microbiome by phenomena such as antibiosis (Suryanarayanan 2013; Kusari et al. 2012; Schulz et al. 2015). Interactions with endophytes enhance the fitness of the plant hosts by increasing their tolerance to abiotic (Redman et al. 2002) and biotic stressors (Mejía et al. 2008; van Bael et al. 2009; Bogner et al. 2016).

Endophytes are well suited for aiding technological advances in various realms due to their capacity to increase the ecological fitness of the plants they colonize, as well as their extraordinary synthetic and catalytic abilities. However, this promise has not been realized because of various reasons including an inadequate knowledge of their ecology and behavior *in planta* (Suryanarayanan 2013). Here, we first address some of the expected payoffs and the roadblocks that have retarded progress and conclude by presenting some future directions that could potentially lead to broad use of endophytes for improving crop yields and producing bioactive metabolites/industrial enzymes.

## 15.2 Potential Applications of Endophytes

### 15.2.1 Improving Plant Fitness

#### 15.2.1.1 Biotic Stress

Association with endophytes aids the plant hosts to tolerate various biotic stressors. For example, leaf-cutting ants, a major defoliator of neotropical plants, avoid endophyte-infected leaves; such benefits offset the cost incurred by the plant in hosting endophytes (Estrada et al. 2015). The exact mechanism of insect deterrence by endophytes is not known but likely includes the production of secondary metabolites that are toxic/distasteful to the insects or by fitness reduction of insects (Bittleston et al. 2011). As some fungal pathogens of insects (entomopathogenic fungi) also occur as endophytes, inoculating crops with these fungi to function as biocontrol agents has been attempted with some success. Lopez et al. (2014) reported that introducing entomopathogenic endophytes *Purpureocillium lilacinum* and *Beauveria bassiana* in cotton inhibited aphid reproduction in greenhouse and field conditions. But cotton plants that experience fewer insect visitations support a lower endophyte load in their tissues (Suryanarayanan et al. 2011), suggesting a positive correlation between insect damage and density of endophyte colonization of plants. Endophytes reduce disease severity caused by fungal pathogens by upregulating many defense-related genes of the plant host (Arnold and Herre 2003; Mejía et al. 2014; Waqas et al. 2015). The mechanism of endophyte-mediated disease tolerance is not well understood. For instance, a *Colletotrichum* strain confers disease tolerance to its host plant by inducing the plant's defense mechanism but only in the presence of the pathogen (Redman et al. 1999). *Piriformospora indica*, a root endophyte of many plants, confers resistance to some pathogens by stimulating the host's OXII pathway, which in turn activates downstream defense pathways (Camehl et al. 2011). In another example, a *Trichoderma* root endophyte induces resistance to root nematode infection by modifying the hormone signaling network of the host plant (Martínez-Medina et al. 2016). Interestingly, competition between plants is influenced by resident endophytes. Inoculation of *Centaurea stoebe* (spotted knapweed) with the endophyte *Alternaria alternata* increases the allelopathic effects of the host plant against *Koeleria macrantha* (bunchgrass) by stimulating secondary metabolite production (Aschehoug et al. 2014).

#### 15.2.1.2 Abiotic Stress

For most crops, more than 50% of yield losses can be attributed to one or more abiotic stresses (Boyer 1982; Bray et al. 2000). Because endophytic fungi confer to their respective host plants tolerance to a range of abiotic stresses such as drought, salinity, extreme temperatures (hot and cold), heavy metal toxicity, and oxidative stresses, they merit consideration as a strategy to alleviate productivity losses. Rodriguez et al. (2008), who termed these associations as “habitat-adapted symbiosis,” have argued that endophytes adapt to stress in a habitat-specific manner and

confer stress tolerance to their respective hosts. Indeed, this expectation has been borne out as illustrated below with specific examples.

*P. indica*, which was isolated from the rhizosphere of plants growing in deserts, confers drought tolerance in plants. This fungus stimulates the expression of several drought stress-related genes in leaves and imparts drought tolerance to various plants, including *Arabidopsis* and Chinese cabbage (Sherameti et al. 2008a, b; Sun et al. 2010). *Trichoderma hamatum* DIS 219b, isolated from *Theobroma gileri*, promoted growth and delayed the onset of drought response in *Theobroma cacao* (Bae et al. 2009). Among the various mechanisms leading to drought tolerance, endophytes have been shown to influence osmoregulation of tissues (Nagabhyru et al. 2013; Song et al. 2015), regulation of stomatal conductance, and maintenance of cell-wall elasticity (Malinowski and Belesky 2000).

Association of plants with endophytes also ameliorates salinity stress (Rodriguez et al. 2008; Singh et al. 2011). The gibberellic-acid producing fungal strains, *Penicillium funiculosum* and *Aspergillus fumigatus*, significantly improved growth of soybean under moderate-/high-salinity stress (Khan et al. 2012). In the presence of the endophyte, the host plant reprograms its salinity-stress response by regulating phytohormones and antioxidant enzymes (peroxidases, catalases) that scavenge reactive oxygen species to minimize cellular toxicity from the secondary oxidative stress (Khan et al. 2015a, b; Rodriguez et al. 2008).

Endophytes are also known to impart thermotolerance to plants, as first documented following studies on *Curvularia protuberata* and its host *Dichanthelium lanuginosum* (panic grass), which thrives in geothermal soils (Redman et al. 2002; Rodriguez et al. 2008). The presence of a double-stranded RNA mycovirus called the *Curvularia* thermal tolerance virus (CThTV) in the endophyte is essential for heat tolerance of both the fungus and its host plant (Marquez et al. 2007; Morsy et al. 2010). While neither the plant nor the fungus can grow at temperatures exceeding 38°C, this three-way symbiosis permits survival at soil temperatures as high as 65°C (Marquez et al. 2007; Morsy et al., 2010). In another example, spores of endophytes from fire-prone forests in India were shown to survive exposure to 115°C (Suryanarayanan et al. 2011); it would be interesting to determine how this trait influences the distribution and diversity of endophytes in fire-prone forests as well as the benefits to hosts. Endophytes have also been shown to impart tolerance to low-temperature stress. Cold-stress tolerance was conferred to germinating rice seeds under laboratory conditions by TempSym1 *Curvularia protuberata*, which was isolated from *D. lanuginosum* (Redman et al. 2011). *C. protuberata* and *Fusarium culmorum*, as endophytes, enhanced the growth, biomass, and yield of rice plants both in the presence and absence of cold, drought, or salt stress (Redman et al. 2011).

### 15.2.1.3 Nutrition Management

Endophytes help the host plants better assimilate nutrients like phosphorus, sulfur, magnesium, calcium, and potassium. Root endophytes enhance nitrogen uptake by plants growing in nitrogen-depleted soil (Upson et al. 2009). The root endophyte *P. indica* enhances phosphate uptake of its host plant by increasing the expression

of phosphate transporter PiPT (Yadav et al. 2010). The dark septate-root endophyte *Heteroconium chaetospira* transfers nitrogen from decaying organic matter in the soil to the roots of *Brassica campestris* (Usuki and Narisawa 2007). A *Colletotrichum tofieldiae* endophytic in the roots of *Arabidopsis thaliana* spreads systemically into the shoot and aids phosphorous uptake only under phosphorous-limiting condition, suggesting that the nutrient-deficient condition might have shaped the transition from a pathogenic to an endophytic form (Hiruma et al. 2016). Indeed, mutation of genes controlling disease development in a pathogenic fungus strain could lead to the conversion to an endophytic strain (Fesel and Zuccaro 2016).

Unlike the well-known role of mycorrhizal fungi in nutrient uptake, the mechanism by which fungal endophytes enhance nutrient assimilation is unclear. Endophytic fungi may promote nitrogen and phosphate uptake by altering plant metabolism and the quality of root exudates and stimulating root growth (Johnston-Monje and Raizada 2011). Also, endophytes could degrade complex compounds to simpler molecules that are more readily bioavailable to plant roots (Porrás-Alfaro and Bayman 2011).

## 15.2.2 *Producing Secondary Metabolites and Industrially Important Enzymes*

### 15.2.2.1 Secondary Metabolites

As might be predicted from the ability of endophytes to modulate plant host responses to various stresses, these fungi synthesize a large number of secondary metabolites with unique molecular architectures and novel bioactivities. The diverse chemical compounds produced by endophytic fungi far exceed those produced by their soil relatives (Nisa et al. 2015) and represent a valuable source of bioactives with potential for drug discovery, as well as industrial and agricultural use (Demain 1999; Keller et al. 2005; Strobel 2006; Porrás-Alfaro and Bayman 2011). These fungi produce a large number of metabolites in culture, including alkaloids, steroids, terpenoids, isocoumarins, quinones, flavonoids, phenylpropanoids, lignans, peptides, phenolics, aliphatics, and volatile organic compounds (Tan and Zou 2001; Gunatilaka 2006; Zhang et al. 2006). Several endophytes have also been explored as important sources of antibiotics (Strobel et al. 1999; Li et al. 2000); antivirals (Guo et al. 2000), antidiabetics (Zhang et al. 1999), antimalarials (Kaushik et al. 2014), antioxidants (Pimentel et al. 2011), and anticancer agents (Chen et al. 2016). Some endophytes even elaborate volatile antifungal compounds (Stinson et al. 2003).

An intriguing feature of many endophytes is their ability to produce an array of secondary metabolites that mimic those produced by their respective host plants, including taxol, camptothecin, podophyllotoxin, vinblastine, hypericin, diosgenin, azadirachtin, and rohitukine (Shweta et al. 2013a, b; Mohana Kumara et al. 2013, 2014). Although genetic cross talk between the plant and the endophyte appears likely, the exact mechanism by which the endophytes are able to produce this spectrum of plant secondary metabolites is unclear (Kusari et al. 2011; Heinig et al. 2013; Mohana Kumara et al. 2013; Sachin et al. 2013; Vasanthakumari et al. 2015).

Another attribute related to secondary-metabolite production by endophytes is their ability to transform non-native molecules. This biotransformation capability might aid the endophyte to detoxify defense compounds of the plant host and to survive in the host tissue, where there is competition with other microbes (including co-occurring endophytes). Some endophytes perform stereoselective biotransformations (Borges et al. 2007). For example, *Phomopsis* sp. converts (-)-grandisin, a tetrahydrofuran lignan, to 3,4-dimethyl-2-(4'-dimethyl hydroxy-3',5'-dimethoxyphenyl)-5-methoxy-tetrahydrofuran, a novel compound with trypanocidal activity (Verza et al. 2009). A *Phomopsis* sp. endophytic in *Pinus taeda* biotransforms limonene into several different products (Bier et al. 2017). This remarkable potential of endophytes represents an untapped area to address synthetic organic chemistry challenges related to structural diversity and complexity.

### 15.2.2.2 Industrially Important Enzymes

While the impressive catalytic arsenal of endophytes has been reviewed before (Correa et al. 2014; Suryanarayanan et al. 2012), we focus here on the utility of endophytic fungi to the biofuel industry that seeks sustainable and economical alternatives to fossil fuels. We define some of the challenges in lignocellulosic biomass (LCB) deconstruction and utilization before shining a spotlight on endophytic fungi to support the claim that they must be at the top of the solution space for these long-standing problems (Suryanarayanan et al. 2015).

Farm, energy crop, and forest LCB (a total of nearly 1 billion tons) can provide the feedstock for generating adequate biofuels to replace 30% of petroleum use in the United States (Oakridge National Laboratory 2011). The conversion of such LCB to biofuels comprises three key steps: (i) pretreatment – physical (e.g., milling) and chemical (e.g., ionic liquids, acid, or alkali at high temperatures) methods to increase the accessibility of the LCB sugar polymers to enzymatic depolymerization (Yang et al. 2008); (ii) saccharification – addition of a cocktail of glycosyl hydrolases (GHs) to hydrolyze cellulose and hemicellulose to their constituent monomeric sugars (Wilson 2009; van den Brink and de Vries 2011); and (iii) fermentation – microbial conversion of sugars to liquid fuels (e.g., ethanol) (Fortman et al. 2008). Bottlenecks at and economic/environmental concerns with each of these steps motivate the search for alternatives. LCB, which has a complex structure composed of cellulose (40–50%), hemicellulose (25–35%), and lignin (15–20%), is recalcitrant to degradation and requires harsh pretreatment prior to saccharification (Himmel et al. 2007; Jordan et al. 2012). There is an urgent need to identify “greener” pretreatments that are more environment friendly and less energy intensive than those currently used for LCB deconstruction, and to design/discover novel cell wall-degrading enzymes that are well suited for the newer conditions. Also, the pretreatments now employed generate various by-products that adversely affect downstream steps. Such inhibitors need to be detoxified effectively prior to saccharification and fermentation.

Due to several reasons, endophytic fungi offer excellent prospects to solve the above mentioned problems that have retarded the biomass-to-biofuel enterprise.

First, through millions of years of coevolution with plants, these fungi have become dominant in the plant microbiome. Importantly, they have evolved a catalytic inventory to support their role as primary degraders of LCB. Endophytic fungi, like the plant pathogenic fungi, secrete an ensemble of plant cell wall-degrading enzymes such as cellulases and pectinases to facilitate their penetration and infection of plant tissues (Correa et al. 2014; Suryanarayanan et al. 2012; Prakash et al. 2015). Many endophytic fungi continue to survive in the dead plant tissues and function as pioneer degraders of plant litter before being replaced by other saprotrophic fungi (Korkama-Rajala et al. 2008; Voříšková and Baldrian 2013; Prakash et al. 2015; Szink et al. 2016). This dual-life strategy of being a plant-associated fungal endophyte in living tissue and a saprotroph in dead tissue necessitates increased production of cell wall-degrading enzymes during the shift from a symptomless endophyte in plants to a saprotroph in plant litter. Such fine-tuning of gene expression has been observed for the mutualistic root symbiotic fungus *P. indica* (Zuccaro et al. 2011). Second, in considering the suitability of microbes for solid-state/substrate fermentation (SSF) to produce enzymes for industrial use, it is clear that the physiology of filamentous fungi makes them superior to other microbes (Raimbault 1998). Rapid growth of the fungi during SSF is facilitated by the extension of multiple hyphae and branching, as well as the active secretion of hydrolytic enzymes by the growing hyphae to promote efficient utilization of the substrate. Third, even in liquid medium, filamentous fungi secrete enzymes at higher levels than yeast or bacteria (Polizeli et al. 2005; Margot et al. 2013). For example, when the white-rot fungus *Trametes versicolor* and the bacterium *Streptomyces cyaneus* were grown in biologically treated wastewater with different carbon sources, the fungus produced 20-fold higher laccase activity than the bacterium (Margot et al. 2013). Last, a broader suite of catabolic options is likely in the larger fungal genomes than in the smaller bacterial ones. The ability of fungi to use a range of carbon substrates might be partly due to an unexpectedly high frequency of interdomain horizontal gene transfers from bacteria to fungi (Bruto et al. 2014) as well as the expansion of specific gene families (Wang et al. 2015a). This fungal genetic repertoire – the key to catalytic versatility and metabolic adaptability – is ripe for exploitation. Given these distinctive attributes, several groups have investigated the utility of endophytic fungi to address problems related to biofuel production. We enumerate select examples below.

### 15.2.2.3 Pretreatment and Saccharification

Cost-effective biofuel production requires efficient degradation of the (hemi)cellulosic fraction of LCB to fermentable sugars. However, lignin, which strengthens cellulose fibrils and lends hardness to the plant cell wall, is a formidable barrier to degradation of cellulose and hemicellulose. Biological pretreatment of LCB with white-rot fungi (basidiomycetes) has been investigated due to the well-documented capacity of these organisms to secrete lignin-degrading peroxidases and laccases (Lopez-Abelairas et al. 2013; Yang et al. 2013). However, endophytic fungi (ascomycetes) isolated from a specific plant/tree might be evolutionarily better adapted for deconstruction of its host biomass than generic wood rot basidiomycetes. Indeed,

*Ulocladium* sp. and *Hormonema* sp., laccase-producing endophytes isolated from eucalyptus trees, fared better than *Trametes* sp. as pretreatment agents, an inference based on their ability to increase saccharification of eucalyptus wood chips (Martin-Sampedro et al. 2015a). In fact, the delignification activities of these endophytes proved valuable during eucalyptus kraft pulping; they reduced the alkali requirement and increased the mechanical strength of the end product (Martin-Sampedro et al. 2015b). Thus, customized pretreatment strategies using endophytes isolated from a target biomass are likely to benefit various industrial applications.

As part of the panel of pretreatment options, ionic liquids (ILs), which are molten organic salts with melting points  $<100$  °C, have drawn attention for their remarkable ability to dissolve biomass (Liu et al. 2012). For instance, cellulose can be selectively dissolved in an IL and then precipitated with an antisolvent like ethanol. The regenerated cellulose shows a 50-fold improved accessibility to cellulase, primarily due to loss of the crystalline structure of cellulose upon IL treatment (Dadi et al. 2006). However, the residual IL (~10–20%) in the recovered cellulose inactivates commercial mixtures of biomass-degrading enzymes (Turner et al. 2003; Gladden et al. 2011). Here, marine-derived fungal (MDF) endophytes warrant closer examination for the presence of salt- or ionic-liquid-tolerant cell wall-degrading enzymes. Since some seagrasses contain up to 40% xylan (Davies et al. 2007), we postulated that their resident endophytic fungi may have evolved efficient mechanisms for xylan degradation (Thirunavukkarasu et al. 2015). Indeed, MDF endophytes isolated as endophytes from marine algae and sea grasses in the Bay of Bengal (southern India) produce xylanases and xylosidases (Thirunavukkarasu et al. 2015). Furthermore, we have recently discovered that some of these enzymes are tolerant of salt (1.2 M) and ionic liquids ( $\leq 20\%$ ) for 48 h (Sengupta, Suryanarayanan and Gopalan, unpublished data). Additional investigations are required to fully compare the properties of these MDF-derived enzymes with commercial cocktails and other recently discovered ionic liquid-tolerant glycosyl hydrolases (Adsul et al. 2009; Datta et al. 2010, Gladden et al. 2014). Regardless, undertaking a systematic exploration of the catalytic spectrum of MDF endophytes may prove gainful for uncovering new ionic liquid-tolerant enzymes.

Given the diversity and heterogeneous nature of LCB in plants of various lineages, having a palette of enzymes from wide-ranging sources (especially fungal endophytes) will be critical for augmenting the limited repertoire of commercially available cell wall-degrading enzymes. Indeed, this objective has stimulated several investigators to conduct bioprospecting in different parts of the world with the expectation of identifying highly active and stable catalysts for biomass degradation. We cite a few examples to highlight the types of studies reported. From 14 plants (e.g., rose, hop) in the Botanical Garden of Hokkaido University, Japan, 169 endophytic fungi were isolated. Nearly 92% of these fungi were found to produce xylanase, even though the isolation procedures did not select for this activity (Suto et al. 2002). Similarly, a majority of the 21 endophytic isolates from *Brucea javanica*, a woody shrub native to southeast Asia, displayed cellulase activity and were able to cause weight loss in wood blocks (Choi et al. 2005). Exploiting the large collection of fungi isolated from natural habitats in Thailand and available through

a national repository, a thermotolerant cellobiohydrolase (active between pH 3 and 11) and  $\beta$ -glucosidase were identified in *Fusicoccum* sp. and *Periconia* sp., respectively (Kanokratana et al. 2008; Harnpicharnchai et al. 2009); notably, this  $\beta$ -glucosidase could augment the activity of a commercial preparation to hydrolyze rice straw. Similarly, when 110 endophytic fungi in the culture collection at the Federal University of Parana, Brazil, were investigated for their ability to grow on media containing the liquor from hydrothermal pretreatment of sugarcane bagasse (a rich source of xylo-oligosaccharides), six fungi – including *Aspergillus niger* and *Trichoderma atroviride* – were identified as the most promising on the basis of the levels of hydrolytic enzymes that they produced (Robl et al. 2013).

#### 15.2.2.4 Bioabatement

A major drawback of subjecting LCB to dilute acid at high temperature, a widely used pretreatment, is the generation of various by-products that adversely affect downstream steps. In addition to a semisolid fraction of amorphous cellulose and lignin, the supernatant contains soluble sugars, as well as weak organic acids (e.g., acetic acid), phenolic derivatives (e.g., vanillin), and furaldehydes (e.g., furfural) (Palmqvist and Hahn-Hägerdal 2000). Furaldehydes hinder efficient biomass utilization by decreasing cellulolytic saccharification (Jing et al. 2009), as well as microbial growth and fermentation efficiency (Klinke et al. 2004; Almeida et al. 2009; Mills et al. 2009). These inhibitors can be removed from biomass hydrolyzates by washing and alkali treatment or by ion exchange (Almeida et al. 2009; Nilvebrant et al. 2001). These methods are expensive and have other drawbacks such as generation of large quantities of wastewater, incomplete removal of inhibitors, and loss of fermentable sugars. These issues have inspired the search for other options.

Bioabatement using microorganisms that can metabolize these LCB-derived inhibitors, preferably with some selectivity over sugars, is a potentially environment-friendly and cheaper route to detoxify lignocellulosic liquors. In this regard, various fungi including *Coniochaeta ligniaria* (Lopez et al. 2004), *Aspergillus niger*, and *Trichoderma reesei* (Rumbold et al. 2009), *Amorphotheca resiniae* ZN1 (Zhang et al. 2010), as well as *Chaetomium globosum*, *Cunninghamella elegans*, *Mortierella isabellina*, and *Mucor plumbeus* (Zheng et al. 2012) have been shown to grow using either furfural or hydroxymethyl furfural (HMF) as the sole carbon source. Similarly, when we recently investigated endophytic and litter fungi of fire-prone dry forests in the Western Ghats (in southern India) for their ability to utilize furaldehydes, we were surprised to find that of 23 (11 endophytic and 12 litter) fungi tested, 10 grew on furfural, 21 on HMF, and 9 on both furfural and HMF. Some of these fungi (e.g., *Pestalotiopsis* sp., *Phomopsis* sp.) showed innate adaptation competence as evidenced by their faster growth on furaldehydes following an initial exposure (Govindarajulu et al. 2014). These findings suggest that locales of biomass (including crop residue) burning are worth exploring to identify new furaldehyde-utilizing fungi. However, before such fungi can be used for selective removal of furaldehydes from LCB hydrolyzates, it will be essential to design sugar-transport mutants to ensure that feedstock sugars for microbial fermentation are not depleted from the hydrolyzates.

## 15.3 Translational Research of Endophytic Fungi: Constraints and Opportunities

### 15.3.1 Improving Plant Fitness

Using endophytes to enhance crop performance involves introduction and establishment of the candidate fungus in the target crop (Chaves et al. 2012; Parsa et al. 2016). Albeit straightforward, there are many impediments to achieve this goal and, not surprisingly, these studies remain at the exploratory level. We consider a few reasons for the lack of progress. Different endophyte species coexist in a leaf, with all of them competing for resources leading to endophyte-endophyte, endophyte-plant host, endophyte-leaf pathogen/pest, and endophyte-epiphyllous organism interactions (Suryanarayanan 2013). However, most investigations that strive for endophyte-mediated enhancement of crop performance use a single endophyte. Such a strategy is unlikely to be gainful given the failure to fully mimic the plant-tissue microhabitat. Hence, a thorough understanding of the ecology of endophytes and *in planta* community structure is essential for reaping benefits associated with endophytes.

An endophyte is unable to easily infect a leaf of another plant species unless at least some of the native endophytes are eliminated (Mohandoss and Suryanarayanan 2009); similarly, an alien endophyte when introduced into a crop is excluded with time (Suryanarayanan 2013). Such elimination is not unanticipated given the coevolution of long-standing endophytes with specific hosts. For example, endophytes residing in the camptothecin-producing plant *Camptotheca acuminata* are resistant to camptothecin (Liu and Reinscheid 2004); such a mechanism minimizes interspecific competition among endophytes in this plant. An endophyte, albeit only one member of a multispecies assemblage in a leaf, can effectively shape the metabolism of the host plant to its near-exclusive benefit. For instance, a taxol-insensitive endophyte increases production of taxol (a fungicide) by the plant host through transcriptional activation of taxol synthesis genes (Soliman et al. 2013). These findings suggest that a native endophyte is able to compete effectively in its host milieu. Indeed, compared with mycorrhizae, the major drawbacks of using endophytes in nutrient management of crop plants stem from the same rationale: most often, the endophytic association is host genotype specific. As described earlier, endophytes suffer from poor establishment in new hosts in part due to competition from endogenous microbes (Johnston-Monje and Raizada 2011).

Although endophytes are closely related to phytopathogenic fungi (Hyde et al. 2009; Zhang et al. 2009; Slippers et al. 2013), they have not received as much attention as the pathogens. Many fungi of the order *Phaeomoniellales* are pathogenic in angiosperms but are endophytic in gymnosperms (Chen et al. 2015). Similarly, *Leptospherulina crassiasca*, the causative organism of pepper-spot disease of peanut in many parts of the world, survives as a symptomless endophyte in leaves of many varieties of peanuts cultivated in the state of Tamil Nadu, southern India (Suryanarayanan and Murali 2006). Whether environmental factors or genotypic variations in plants lead to these dramatic changes is unclear, but lack of a full understanding of these variables poses yet another challenge to endophyte-mediated crop-improvement strategies.

In contrast to pathogenic fungi, it remains unclear how a suite of endophytes remain symptomless and escape elimination by the host plant; adding further intrigue is the upregulation of numerous defense genes of the host plant after an endophyte infection (Mejía et al. 2014). The “balanced antagonism” mechanism was proposed by Schulz et al. (1999) to explain this somewhat puzzling observation. Plants initially recognize microbes, including fungi as pathogens, and allow mutualistic associations only when fitness benefit accrues (Schulz et al. 1999; Liberman and Benfey 2016). The recent work of Hiruma et al. (2016) showed that in Brassicaceae (*Arabidopsis*) plants, which do not support a mycorrhizal association, phosphate acquisition is mediated by *Colletotrichum tofieldiae*, a root endophyte. Here, there is a clear threshold set by the plant to ensure an exquisite balance between benefits and costs. In mutant *Arabidopsis* plants that are unable to synthesize tryptophan-derived antimicrobials, extensive *C. tofieldiae* growth culminates in the death of the plant. Although a model plant, *Arabidopsis* could be used to answer many questions regarding endophytism before extending to studies of crop plants (Suryanarayanan 2013).

Infection of roots by mycorrhizal fungi enhances the defense of plant hosts to infection by pathogens through the phenomenon of induced systemic resistance (Pieterse et al. 2014). The possible role of such induced resistance conferred by endophytes has to be investigated further especially since avirulent strains of a plant pathogenic fungus could survive as endophytes in a plant (Kavroulakis et al. 2007). Collectively, the earlier studies indicate that a multitude of dynamic interactions could be operating in a leaf colonized by a suite of endophytes. Therefore, studying the interaction between a plant host and one of its endophytes will not suffice to implement endophyte-mediated crop improvement. Factors governing the interaction between different endophytes in the plant tissue and their host, as well as with other entities of the plant microbiome (endophytic bacteria, pathogens, herbivores), are critical to move forward. Equally important is a knowledge of establishment and persistence of an alien endophyte obtained from a noncrop source in a given crop plant.

### **15.3.2 Producing Secondary Metabolites and Industrially Important Enzymes**

#### **15.3.2.1 Secondary Metabolites**

Endophytes synthesize many novel bioactive metabolites (Krohn et al. 2008; Kharwar et al. 2011), including some generated by their plant hosts (e.g., taxol; Sachin et al. 2013). Although one might expect that subculturing the endophytes would afford a biosynthetic route, attempts so far have been unsuccessful due to the low quantity of metabolites produced. Strain modification, metabolic engineering, and induction of cryptic genes are being considered as alternatives to sustain the production of bioactives by endophytes in culture. Because the synthetic potential of an endophyte is expected to be high in the competitive plant-tissue microhabitat (Rodríguez et al. 2012), an understanding of the functional plasticity of endophytes in plants would enhance the utility of endophytes as microbial factories for

producing bioactives. For example, coculturing of fungi might engender synthesis of bioactives not possible by individual members of fungal consortia (Bertrand et al. 2013). An interplay of co-metabolism and biotransformation could be expected in coculturing experiments resulting in the synthesis of novel bioactives (Borges et al. 2007; Pimentel et al. 2011). *Colletotrichum fructicola* and *Corynespora cassiicola*, two endophytes isolated from *Nothapodytes nimmoniana*, produce camptothecin in submerged cultivation at significantly higher levels when cultured together than when grown independently (Bhumika et al. 2016). Paranetharan, Thirunavukkarasu, and Suryanarayanan (unpublished) found that some mangrove root endophytes produce anti-algal metabolites when cocultured but not while growing as axenic cultures. An additional consideration arises from the fact that bacteria occur as endophytes along with fungi: thus, studying fungal endophytes in isolation may not lead to the complete realization of their synthetic potential (van Overbeek and Saikkonen 2016).

Fungal endophytes, like other ecological groups of fungi, support bacteria and viruses within their cells. Such endohyphal bacteria are widespread in endophytes (Hoffman and Arnold 2010). The interactions between endohyphal bacteria and endophytes, as well as their consequences on host plants, are not known. Hoffman et al. (2013) reported that IAA production by a foliar endophytic fungus increases when it houses an endohyphal bacterium. As expected, the culture filtrate obtained from growing this endophyte containing the resident bacterium increased the growth of test plants more than that of the filtrate from the endophyte alone. These observations highlight the importance of understanding the ecology of endophytes for harnessing their useful traits.

### 15.3.2.2 Industrially Important Enzymes

While the potential of fungal endophytes to aid the biofuel industry is unquestioned, prioritizing objectives will ensure expedient payoffs. We suggest directions for each of the three major steps during the production of biofuels [pretreatment, saccharification, and (bioabatement preceding) fermentation].

Once the type of abundant biomass in a given geographic locale is identified as the most likely feedstock for biofuel production, the first goal must be to isolate the resident endophytes (capable of saprotrophic growth) in the chosen biomass. As part of a strategy specifically tailored for this target biomass, these endophytes should be systematically investigated for their delignification capabilities and compared with established pretreatment methods for their ability to improve downstream saccharification. These endophytes might supplement rather than supplant existing methods, with pretreatment dividends arising from use of either decreased alkali/acid or lower temperatures. The next step to enhanced delignification might entail the construction of a second-generation variant by either mutagenesis or overexpression of native laccases and peroxidases in the parental strain.

Endophytic fungi are a treasure trove of biocatalysts, including those highly sought by the biofuel industry for improving saccharification efficiency

(carbohydrate-active enzymes, CAZymes). Screening endophytes associated with plants of different harsh and less-studied habitats for novel biomass-degrading enzymes is likely to be profitable. To accelerate the discovery and design of novel enzymes with high activity and stability over a wide range of pH and temperatures, and preferably with tolerance to ionic liquids, we consider biochemical characterization and protein engineering of CAZymes identified by genome sequencing and transcriptomic/proteomic efforts. For example, sequencing the industrial strain *Aspergillus niger* CBS 513.88 identified 281 putative polysaccharide-degrading enzymes representing 61 different enzyme families involved in cellulose degradation (Pel et al. 2007). Similarly, sequencing of *Pestalotiopsis fici*, a fungal endophyte, revealed 460 GHs and 121 glycosyl transferases (GTs) (Wang et al. 2015a). While these rich databases offer a starting point for choosing CAZymes that merit tinkering for industrial applications, priority must be given to candidates identified by gene expression studies. For example, transcriptomic analysis of *Neurospora crassa* grown on cellulose revealed upregulation of genes encoding cellulases, hemicellulases, carbohydrate esterases, glucosidases, xylosidases, and other members of the CAZyme family (Tian et al. 2009). The most ideal approach would be to perform transcriptomic and proteomic studies on fungi grown on a desired biomass feedstock to determine the most relevant secreted lignocellulolytic enzymes, as exemplified in a recent study on *Pestalotiopsis* sp. isolated from a mangrove (Arfi et al. 2013). Wood chips from *Rhizophora stylosa* mangrove trees were used to support the growth of *Pestalotiopsis* sp. De novo transcriptome sequencing and assembly, followed by comparison with the CAZy database, revealed an impressive array of 238 GHs, 82 GTs, and 53 lignolytic enzymes. Moreover, of 209 proteins confidently identified from a proteomic analysis of the secretome, 40% and 15% corresponded to glycosyl hydrolases and lignolytic enzymes, respectively.

Despite extensive bioprospecting to identify glycohydrolases that function efficiently at physical/chemical extremes, the key for industrial use of these newly identified enzymes is to rein in production costs. Indeed, techno-economic analyses indicate that market viability of lignocellulosic biofuels will require a significant effort to lower the cost of saccharification enzymes (Klein-Marcuschamer et al. 2012). In this regard, with a target waste material (e.g., crop residue, seagrass/seaweed detritus) as the substrate in SSF medium for growth of endophytic fungi, it should be possible to induce the expression of appropriate (hemi)cellulolytic enzymes and isolate the enzyme-rich secretomes (Thirunavukkarasu et al. 2015). This low-cost approach would also help mitigate environmental pollution by finding use for solid waste and offering a nonrecombinant alternative for production of enzyme cocktails. A SSF study of *Penicillium janthinellum* mutants, generated by treatment with ethyl methyl sulfonate (a chemical mutagen) and UV irradiation, provides a valuable precedent in this regard (Adsul et al. 2009). Using steam-exploded sugarcane bagasse in combination with wheat bran in SSF led to production of high levels of endoglucanase [3710 international units (IU)/g carbon substrate], xylanase (3230 IU/g carbon substrate), and  $\beta$ -glucosidase (155 IU/g carbon substrate) by one of the *P. janthinellum* mutants; these values represent a 5-, 13-, and 1.5-fold increase in endoglucanase, xylanase, and  $\beta$ -glucosidase activities,

respectively, compared to the parental wild-type strain. Importantly, these enzymes showed unanticipated tolerance to ionic liquid [even up to 50% (v/v)]. While the molecular changes that led to this remarkable outcome in a *P. janthinellum* mutant are unclear, this study demonstrates how a target fungus with desired properties could be further improved by standard mutagenesis methods. Moreover, to increase the production rate of CAZymes by fungi during SSF, identification of the optimum growth phase and regulatory control mechanisms are essential. Since fungal cellulases and xylanases are subject to transcriptional control (Van Peij et al. 1998; Battaglia et al. 2011), design of small-molecule transcriptional activator mimics to enhance gene expression is likely to be profitable. Also, by use of crude secretomes, the perils of reductionist approaches are avoided – a single recombinant glycosidase may fail to mimic the efficiency of catalytic ensembles in the secretome.

Additional work is required to exploit the promise of (endophytic) fungal bioabatement strategies to detoxify inhibitors arising from LCB pretreatment. Foremost, the metabolic pathways for utilization of these compounds (e.g., furaldehydes, phenolics) need to be established. RNAseq is a powerful tool to monitor differential gene expression. By growing fungi in the presence of either glucose or furfural, those genes upregulated in the presence of furfural could provide clues as to the utilization routes. In fact, the transcriptomic analyses of *Amorphotheca resiniae* ZN1 grown in the presence of furfural or HMF led to identification of several upregulated alcohol dehydrogenases and alcohol reductases (Wang et al. 2015b). These data highlight parallels with bacteria where furaldehydes are sequentially oxidized to their alcohols and acids before eventual conversion to  $\alpha$ -ketoglutarate (Koopman et al. 2010). While overexpression of such key genes involved in furaldehyde metabolism will result in a fungus with superior detoxification, this advance, however, requires that the bioabatement-enabling fungus is amenable to genetic manipulation, including downregulation of its hexose/pentose transporters. Moreover, because industrial settings require low pH and anaerobic conditions, it has been pointed out that the oxygen-requiring aerobic bacterial pathways for furfural utilization are not readily usable (Wierckx et al. 2011). If the fungal pathway for utilization of furfural/HMF differs from the bacterial route in its oxygen requirement, it might be feasible to transfer the genes encoding the furfural catabolic pathway to anaerobic fungi, such as those isolated from rumen and now being evaluated for their lignocellulosic degradation capabilities (Youssef et al. 2013).

## 15.4 Envoi

While advances from numerous genome sequencing and tool development (e.g., RNAi, CRISPR) initiatives will undoubtedly be valuable, the use of culture-independent strategies and “omics” approaches to study endophyte diversity may prove decisive as to the future trajectory of endophyte research and applications. Most studies on endophytes have so far dealt with only the easily cultivable fungi, leaving behind slow growing and unculturable endophytes; simulated natural

environments for culturing deserve a closer look. As elaborated earlier with numerous examples, failure to characterize the community-level endophytic complexity has already undermined the promise of several approaches for crop improvement and secondary-metabolite generation. Thus, there is some urgency to spatiotemporal sampling of endophytes in the plant host in order to appreciate the dynamic changes in the community structure (Suryanarayanan and Thennarasan, 2004) and to channel this knowledge through an understanding of “why the whole is greater than a sum of its constituent endophytes.”

With regard to specific applications such as those of interest to the biofuel industry, bioprospecting exercises have proven the value of broad-scope exploration while providing guiding principles for a future roadmap. For instance, identification of endophytes in target biomasses specifically selected as feedstocks for a geographic locale should be followed by an evaluation of their potential to improve pretreatment, saccharification, and bioabatement (Suryanarayanan et al. 2015). Additionally, the idea of using detritus or other types of waste as solid-state substrates for associated persistent endophytes to produce biocatalysts at low cost deserves serious consideration. New tools for genome editing of fungi only heighten the prospects for exciting advances from such pursuits.

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