CURRENT REVIEW

Sniffing on Microbes: Diverse Roles of Microbial Volatile Organic Compounds in Plant Health

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Secreted proteins and metabolites play diverse and critical roles in organismal and organism–environment interactions. Volatile organic compounds (VOC) can travel far from the point of production through the atmosphere, porous soils, and liquid, making them ideal info-chemicals for mediating both short- and long-distance intercellular and organismal interactions. Critical ecological roles for animal- and plant-derived VOC in directing animal behaviors and for VOC as a language for plant-to-plant communication and regulators of various physiological processes have been well documented. Similarly, microbial VOC appear to be involved in antagonism, mutualism, intra- and interspecies regulation of cellular and developmental processes, and modification of their surrounding environments. However, the available knowledge of how microbial VOC affect other organisms is very limited. Evidence supporting diverse roles of microbial VOC with the focus on their impact on plant health is reviewed here. Given the vast diversity of microbes in nature and the critical importance of microbial communities associated with plants for their ecology and fitness, systematic exploration of microbial VOC and characterization of their biological functions and ecological roles will likely uncover novel mechanisms for controlling diverse biological processes critical to plant health and will also offer tangible practical benefits in addressing agricultural and environmental problems.

Every organism employs a network of signaling pathways to sense the environment and other organisms and to launch one or more specific molecular, cellular, or developmental changes. This signaling mechanism ensures cellular homeostasis, directs orderly growth and development, and controls behavior. Because sensing of the environment and other organism occurs often through the recognition of specific molecules, a vast array of secreted proteins and metabolites play key roles in these mechanisms. In turn, many organisms also have evolved the ability to exploit these mechanisms in other organisms to benefit themselves or coordinate symbiosis (Bednarek et al. 2010;

Bonfante and Anca 2009). The following examples illustrate the critical significance of secreted molecules for the health and fitness of plants: i) manipulation of physical and chemical properties of soil (e.g., organic acids to facilitate phosphorus acquisition and to chelate toxic heavy metals) and ii) control of interspecies interactions (e.g., allelopathy; volatile compounds to attract pollinators, seed dispersers, and parasitoids of herbivorous insects; antimicrobial compounds and proteins for defense; flavonoids to initiate the formation of symbiosomes by rhizobia; and strigolactones for mycorrhizal symbiosis).

Plant-associated microbes also secrete various molecules that affect plant health both directly and indirectly (Bednarek et al. 2010; Bonfante and Anca 2009): i) altering physical and chemical properties of their immediate surroundings to increase nutrient availability for themselves and associated plants (e.g., siderophores for iron acquisition and enzymes and metabolites to facilitate phosphorus acquisition), ii) antagonizing pathogenic organisms (e.g., antibiotics and antimicrobial proteins), and iii) priming host cells for subsequent colonization (e.g., modulation of external pH to facilitate pathogenesis and molecules that coordinate symbiosis or quorum sensing). Pathogenic microbes secrete assorted virulence factors (or effectors) into plant–pathogen interspaces and the cytoplasm of host cells via specialized secretion systems, in order to attenuate host defense responses and support pathogen proliferation (Martin and Kamoun 2012). Plants have evolved to recognize certain pathogen-derived molecules as signals in the species- or isolate-specific (e.g., avirulence factors) and non-species-specific (e.g., fungal cell wall components and bacterial flagella and lipopolysaccharides) manners in order to initiate rapid and strong defense responses (Thomma et al. 2011). Collectively, molecules secreted by plants and microbes affect the structure and emergent properties of plant-associated microbial communities as well as the health of plants and soils (Bednarek et al. 2010; Berendsen et al. 2012; Lundberg et al. 2012).

Organisms ranging from microbes to animals to plants secrete volatile organic compounds (VOC) that affect their environments and each other (Fig. 1) (Baldwin 2010; Effmert et al. 2012; Herrmann 2010; Kramer and Abraham 2012; Morath et al. 2012; Schulz and Dickschat 2007). Biogenic VOC exhibit certain common chemical and physical properties: they i) belong to chemical classes such as alcohols, thiols, aldehydes, esters, terpenoids, and fatty acid derivatives; ii) are usually lipophilic; and iii) have low molecular weight (<300 Da) and high vapor pressure (0.01 kPa or higher at 20°C), such that they evaporate easily at normal temperatures and pressures (Schulz and Dickschat 2007). VOC are often less diverse than

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*The e-Xtra logo stands for “electronic extra” and indicates that Figure 1 appears in color online.

nonvolatile compounds secreted by individual organisms, helping in their analysis. Analysis of VOC typically relies on gas chromatography mass spectrometry (GC-MS), which integrates the separation capability of GC with MS that can identify and quantify individual compounds. Rapid advances in GC-MS have enabled comprehensive profiling and identification of VOC (Reaves and Rabinowitz 2011; Sardans et al. 2011; Zhang and Li 2010).

Due to their ability to move through air spaces as well as liquids (Effmert et al. 2012), VOC can serve as ideal signaling molecules (semio- or info-chemicals) for mediating both short- and long-distance intercellular and organismal interactions. VOC from animals and their associated microbes guide biting insects to their prey (Baldwin 2010; Ezenwa et al. 2012; Herrmann 2010; Verhulst et al. 2011). Plants are perhaps the most prolific producers of VOC (Baldwin 2010; Clavijo-McCormick et al. 2012; Herrmann 2010). It is estimated that, collectively, plants produce close to 30,000 different VOC using as much as 20% of their fixed CO₂ (Baldwin 2010). Not surprisingly, plant VOC seem to perform diverse and critical functions, one of which is mediating communications with other organisms (Baldwin 2010; Clavijo-McCormick et al. 2012; Wenke et al. 2010). Attraction of pollinators and seed dispersers via the release of VOC by flowers and fruits, respectively, ensures reproductive success. Volatiles released from

tissues damaged by herbivory attract predators and parasitoids of herbivores (Baldwin 2010; Clavijo-McCormick et al. 2012). A recent review outlines how mixtures of herbivore-induced VOC encode specific messages, such as the nature and developmental status of the herbivore, to predators and parasitoids (Clavijo-McCormick et al. 2012). Volatile hormones and hormone derivatives, such as ethylene, methyl jasmonate, and methyl salicylate (Fig. 2), control plant defense responses (Baldwin 2010; Robert-Seilanianantz et al. 2011). These signals also participate in priming neighboring tissues and plants for stronger and more rapid defense responses in case they are attacked (Yi et al. 2010). Some VOC contribute to defense via their antimicrobial activities (Baldwin 2010). For example, tomato leaves treated with chitosan oligosaccharide, a degradation product of the fungal cell wall, induced the production of VOC that inhibit fungal pathogen growth (Zhang and Chen 2009). Spices and herbs are prized for their prolific production of essential oils, which effectively protect against diverse pathogenic microbes (Cheng et al. 2005; Kordali et al. 2005; Soyulu et al. 2007). Some plant VOC also participate in moderating abiotic stresses, such as extreme temperatures, high light intensity, drought, salinity, mechanical damage, and pollutants (Vickers et al. 2009). More comprehensive information about plant VOC and their functions can be found in the following reviews: Baldwin (2010), Clavijo-McCormick and associates

Fig. 1. Known and hypothesized roles of volatile organic compounds (VOC) in mediating organismal interactions within and across kingdoms. The double-headed arrows denote VOC-mediated organismal interactions. Anthropogenic and biogenic VOC enter the surrounding atmosphere, potentially affecting the environmental quality and ecosystem health. Soils function as both sources and sinks of VOC. Certain VOC produced by plant growth-promoting rhizobacteria (PGPR), such as 2,3-butanediol, induce plant growth and stress resistance.

(2012), Heil and Karban (2010), Herrmann (2010), Kant and associates (2009), and Yi and associates (2010).

Similarly, there is increasing evidence that microbial VOC play cognate roles in mediating antagonism, mutualism, intra- and interspecies regulation of cellular and developmental processes, and modification of their surrounding environments. However, compared with plant VOC, our knowledge about the biological and ecological roles of microbial VOC is limited. In this review, we highlight the nature and known or proposed functions of bacterial and fungal VOC with a focus on those that affect plant health directly or indirectly. Due to the space limitation, we are unable to discuss all relevant studies. Rather, we suggest recent review articles as entry points to the topics that are not adequately covered. Moreover, because studies on fungal VOC lag considerably behind those on bacterial VOC, we have allocated more space to the former in hopes of stimulating new research. We also discuss challenges in elucidating the ecological roles of microbial VOC and present potential opportunities for improving plant health through a systems understanding of the mechanisms underpinning VOC-mediated plant-microbe and microbe-microbe interactions.

Microbial VOC as regulators of plant growth and stress resistance.

Diverse groups of bacteria and fungi are intimately associated with plants and their rhizosphere and affect the growth and fitness of plants by modulating processes such as pathogenesis, defense, tolerance to environmental stresses, and nutrient recycling and utilization (Buée et al. 2009; Khan et al. 2009; Saunders et al. 2010). Accordingly, plant-associated microbial communities play critical roles in the ecology of plants at both the individual and community levels (Bever et al. 2010; Inderjit and van der Putten 2010; Porras-Alfaro and Bayman 2011). However, with the exception of a few extensively studied microbes, such as nitrogen-fixing bacteria, mycorrhizal fungi, and major pathogens, the question of how many other microbes affect plants remains to be elucidated. Release of VOC is one of the mechanisms that certain microbes utilize to influence the growth and fitness of associated plants. Here, we review selected examples of how microbial VOC affect plants. Additional examples can be found in recent reviews (Bailly and Weisskopf 2012; Bennett et al. 2013; Wenke et al. 2012b).

VOC produced by several rhizobacterial species enhanced the growth or stress resistance of plants (Ryu et al. 2003).

Fig. 2. Structure of microbial volatile compounds with known effects on other organisms. Compounds produced by **A**, bacteria and **B**, fungi are noted along with their known and suspected functions. ¹Plant growth enhancement, ²increased stress resistance, ³phytotoxicity, ⁴antimicrobial activity, ⁵signal for controlling the growth or development of itself or other microbes, and ⁶chemo-attractant.

Comparison of VOC profiles, application of synthetic compounds, and bacterial mutants defective in producing candidate compounds suggested that 2,3-butanediol (Fig. 2) is a major VOC produced by *Bacillus subtilis* and *B. amyloliquefaciens* to mediate growth promotion in *Arabidopsis thaliana* (Frag et al. 2006; Ryu et al. 2003). Co-cultivation of *A. thaliana* with these *Bacillus* strains in the I plate, a partitioned petri dish that prevents their physical contact, also induced systemic resistance in *A. thaliana* against *Erwinia carotovora*, as did exogenous application of 2,3-butanediol (Ryu et al. 2004). Salt tolerance of *A. thaliana* was also increased by VOC from *B. subtilis* (Zhang et al. 2008a). In addition, isolates of other *Bacillus* spp., cultured from the rhizosphere of lemon plants, affected the growth and root architecture of *A. thaliana* via VOC production; however, the nature of responsible VOC remains unknown (Gutierrez-Luna et al. 2010). *Pseudomonas chlororaphis* also produced 2,3-butanediol and enhanced the growth of tobacco (Han et al. 2006). Its synthesis by *P. chlororaphis* requires the sensor kinase GacS (Han et al. 2006). Given that GacS controls the production of signal molecules such as the acyl-homoserine lactones, 2,3-butanediol and, potentially, other VOC may belong to a cache of chemical signals bacteria deploy to communicate with neighboring organisms. Among three stereoisomers of 2,3-butanediol, only 2R,3R-butanediol was effective in causing these phenotypes (Han et al. 2006), suggesting the presence of specific receptors for this isomer in plants. This compound increased resistance of tobacco against *E. carotovora* but not against *P. syringae* pv. *tabaci* (Han et al. 2006) and also enhanced drought tolerance in *A. thaliana* (Cho et al. 2008). Members of other bacterial genera that are associated with the rhizosphere, such as *Burkholderia cepaci* and *Staphylococcus epidermidis*, also produce VOC that promote the growth of *A. thaliana*, although the specific identity of the causal compounds remains unknown (Vespermann et al. 2007).

Not all bacterial volatiles positively affect plants. Members of several bacterial genera, including *Burkholderia*, *Chromobacterium*, *Pseudomonas*, *Serratia*, and *Stenotrophomonas*, produce several volatiles that inhibit plant growth or exhibit phytotoxicity (Bailly and Weisskopf 2012; Kai et al. 2009). Compounds that likely mediate these negative effects have been identified in a few bacteria and include ammonia, dimethyldisulfide, hydrogen cyanide (HCN), and 3-phenylpropionic acid (Blom et al. 2011b). Interestingly, certain soil bacterial pathogens might use VOC as effectors to suppress host defense responses (Blom et al. 2011a).

By taking advantage of resources available for *A. thaliana*, the mechanisms underpinning bacterial VOC-mediated effects have been studied. Growth responses of *A. thaliana* mutants, defective in one or more hormonal signaling pathway, to *Bacillus* VOC showed that some mutants (*ein2* and *cre1*) responded to VOC from *B. subtilis* but not those from *B. amyloliquefaciens* (Ryu et al. 2003). Similarly, induced resistance against *E. carotovora* by *B. subtilis* VOC required an ethylene-dependent signaling pathway but this pathway was not needed for *B. amyloliquefaciens* VOC (Ryu et al. 2004). Drought tolerance caused by *P. chlororaphis* VOC and 2R,3R-butanediol seems to require the salicylic acid, jasmonic acid (JA), and ethylene signaling pathways (Cho et al. 2008). Decreased stomatal aperture induced by 2R,3R-butanediol, thus reducing water loss, appears to contribute to this phenotype (Cho et al. 2008, 2012). These mutant studies suggest that different strains produce different blends of VOC, consequently requiring different combinations of plant signaling pathways to mediate their effect. Transgenic *A. thaliana* lines expressing β -glucuronidase (GUS) under the promoters that respond to specific hormones have been employed to determine the spatial and temporal

activation pattern of individual hormonal signaling pathways by *Bacillus* VOC, which complemented the mutant studies in evaluating the role of these pathways (Ryu et al. 2004; Zhang et al. 2007). Expression patterns of the genes involved in auxin synthesis, transgenic lines containing GUS driven by a promoter responding to auxin, and plant responses to the auxin transporter inhibitor 1-naphthylphthalamic acid suggest that regulation of auxin homeostasis by VOC is critical for growth promotion (Zhang et al. 2007). However, the involvement of other hormones could not be ruled out. Most of the *A. thaliana* genes that are differentially expressed in response to *B. subtilis* VOC (approximately 600) appear to function in cell wall modification, metabolism, stress responses, or hormone regulation (Zhang et al. 2007). A combination of proteome analysis, reverse-transcriptase polymerase chain reaction, and measurement of the activity of antioxidant enzymes also suggested a number of molecular changes potentially underpinning growth promotion of *A. thaliana* by *B. subtilis* VOC (Kwon et al. 2010). These VOC augmented the efficiency of photosynthesis and chlorophyll content in *A. thaliana* by modulating endogenous sugar and abscisic acid signaling, thus supplying resources needed for enhanced plant growth (Zhang et al. 2008b). Increased salt tolerance conferred by *B. subtilis* VOC requires *HKT1*, an *A. thaliana* gene encoding a high-affinity Na⁺ transporter (Zhang et al. 2008a). Analysis of its expression pattern suggested tissue-specific regulation as a potential mechanism underlying this effect (Zhang et al. 2008a). Under salt stress (100 mM NaCl) in *A. thaliana* exposed to *B. subtilis* VOC, *HKT1* was downregulated in roots but upregulated in shoots, resulting in lower overall Na⁺ accumulation than that in control plants (Zhang et al. 2008a). Little is known about how certain volatiles stunt or kill plants. Oxidative stress caused by HCN, which is produced by a few species, appears to underlie its phytotoxicity (Blom et al. 2011b). Molecular responses of *A. thaliana* to growth-inhibiting VOC from *Serratia plymuthica* and *Stenotrophomonas maltophilia* suggest that one of the WRKY transcription factors, WRKY18, plays a critical role in mediating growth inhibition (Wenke et al. 2012a).

Many plant-associated fungi influence plant processes (Porras-Alfaro and Bayman 2011; Saunders et al. 2010). However, whether fungal VOC play any significant physiological roles in plants remains mostly unknown. Several *Trichoderma* spp. have been extensively studied and commercially utilized because of their ability to compete effectively against pathogenic soil microbes and enhance certain plant performances (Harman 2011; Lorito et al. 2010). Similar to what has been observed in *A. thaliana* treated with certain bacterial VOC, *A. thaliana* exposed to unknown VOC produced by *T. viride* grew taller and bigger, flowered earlier, and had more lateral roots and chlorophylls (Hung et al. 2013). Treatment with 1-octen-3-ol, a VOC commonly produced by fungi through enzymatic modifications of linoleic acid, was shown to induce the expression of several genes under the control of the JA/ethylene-dependent pathogen or wound defense signaling pathway in *A. thaliana* (Kishimoto et al. 2007). Consistent with the gene expression pattern, treated plants exhibited increased resistance against the necrotrophic fungal pathogen *Botrytis cinerea*, suggesting that plants may have evolved to recognize certain fungal VOC as microbe-associated molecular patterns. Unidentified VOC from *Alternaria alternata*, *Penicillium charlesii*, and *P. aurantiogriseum* promoted the accumulation of starch in leaves of several plant species as well as their growth (Ezquer et al. 2010). However, it is not clear as to how the modulation of starch metabolism influences their interactions with plants. *Fusarium oxysporum* is a soilborne fungal species complex that often resides in the rhizosphere of diverse plants, includes vascular wilt pathogens of >100 plant species, and can also be

saprophytic. A nonpathogenic strain of *F. oxysporum*, MSA35, protects plants from pathogenic *F. oxysporum* isolates and is associated with a group of ectosymbiotic bacterial species (Minerdi et al. 2009, 2011). This strain enhanced the growth of lettuce via VOC production (Minerdi et al. 2011). When its symbiotic bacteria had been cured by serially culturing MSA35 in a medium amended with antibiotics, the cured strain could no longer promote plant growth (Minerdi et al. 2011). Comparison of VOC produced by MSA35 and the cured strain showed a difference in the production of some sesquiterpenes (Minerdi et al. 2009). Lettuce seedlings treated with β -caryophyllene (Fig. 2), one of the sesquiterpenes produced by MSA35, displayed phenotypes similar to those exposed to VOC from MSA35 (Minerdi et al. 2011). In contrast, VOC produced by fruiting bodies of the ectomycorrhizal truffles *Tuber borchii*, *T. indicum*, and *T. melanopsorum* inhibited root development and foliar growth of *Arabidopsis thaliana* and their host *Cistus incanus* and, in some cases, caused phytotoxicity (Splivallo et al. 2007). When 10 main truffle VOC tested individually, most of them negatively affected the seed germination, primary root elongation, and leaf growth of *A. thaliana*. In-depth analyses with two VOC, 1-octen-3-ol and trans-2-octenal, suggested that modification of the oxidative metabolism by these VOC might underlie the negative effects on growth (Splivallo et al. 2007).

Given the vast diversity of microbes in and around plants, the number of bacterial and fungal species that have been analyzed for the production of VOC that affect plants is grossly inadequate. Furthermore, the focus of most previous surveys has been on those dwelling in soils, especially the rhizosphere. A systematic survey of microbial communities associated with diverse plants in different ecosystems, including those associated with aboveground parts of plant (e.g., endophytes and phyllosphere microbes), is needed to advance our understanding of the evolution and roles of microbial VOC in modulating plant growth and fitness.

Microbial VOC as chemical weapons against other microbes.

Most microbes reside in their ecological niches in close association with other organisms. The structure and emergent properties of such communities are intimately linked to how their members interact with each other and the environment (Konopka 2009). Competition for nutrients and space probably is the most common form of interaction and often leads to a chemical warfare, in which competing members secrete a diverse array of proteins and compounds to suppress or kill the others. Some bacteria and fungi that are well equipped with such weapons have been exploited as biocontrol agents to manage plant pathogens (Pal and McSpadden Gardener 2007). A main motivation that has driven studies on antimicrobial VOC is the potential utility of VOC and their producers as novel agents for pathogen control. Synthetic and plant-derived VOC already have been extensively utilized to manage insect pests (Thacker and Train 2010). However, although the exploration of antimicrobial VOC started decades ago (McCain 1966), this field still is in its infancy because most studies have focused on discovery, with little known about how antimicrobial VOC affect target microbes.

VOC produced by several bacteria have been shown to inhibit spore germination and mycelial growth or cause abnormal morphological changes in fungi (Effmert et al. 2012). Among 197 bacterial strains cultured from canola and soybean plants, 14 of them, most of which belong to four *Pseudomonas* spp., consistently produced VOC that inhibited germination of sclerotia and ascospores or mycelial growth of *Sclerotinia sclerotiorum*, a major fungal pathogen of these plants, in vitro

and in soil tests (Fernando et al. 2005). Among the 23 volatiles from these isolates, benzothiazole, cyclohexanol, n-decanal, dimethyltrisulfide, 2-ethyl-1-hexanol, and nonanal (Fig. 2) completely inhibited mycelial growth and sclerotial germination. None of the 14 isolates produced all six compounds, indicating that different strains produce different combinations of common and strain- or species-specific antifungal volatiles. A more extensive survey involving 1,018 bacterial isolates showed that VOC from 328 isolates, which belong to families Alcaligenaceae, Bacillales, Micrococcaceae, Rhizobiaceae, and Xanthomonadaceae, inhibited spore germination and mycelial growth of two nematocidal fungi (Zou et al. 2007). Seven VOC, including acetamide, benzaldehyde, benzothiazole, 1-butanamine, methanamine, phenylacetaldehyde, and 1-decene, appear to play roles in fungistasis. Benzothiazole was the only VOC that was found in both surveys, suggesting that different species produce different VOC for fungistasis, antifungal activity of many compounds are target specific, or a combination of both. Although alterations in enzyme activities or gene expression in fungi have been observed upon exposure to certain bacterial VOC in several studies (Effmert et al. 2012), the question of what molecular changes underpin fungistasis has not been clearly answered.

Not surprisingly, fungi also produce VOC exhibiting antibacterial or anti-fungal activity. Some of the VOC produced by the oyster mushroom *Pleurotus ostreatus* inhibited the growth of several bacterial species at concentrations found in its fruit body (Beltran-Garcia et al. 1997). Fungal endophytes confer multiple fitness benefits, including enhanced resistance to biotic and abiotic stresses (Porrás-Alfaro and Bayman 2011), but the underlying mechanisms are poorly understood. Certain endophytes produce antimicrobial VOC which may directly contribute to defense against pathogens. Chokol K, a VOC produced by the grass endophyte *Epichloë* sp., inhibited the growth and spore germination of two mycoparasites associated with stromata, the fruiting structure of *Epichloë* spp., and two plant-pathogenic fungi (Steinebrunner et al. 2008a). *Muscodor albus*, a fungal endophyte originally isolated from cinnamon tree, emits a mixture of VOC that inhibit or kill a broad range of bacteria, fungi, and oomycetes (Strobel et al. 2001). Analysis of its VOC via GC-MS and bioassays with identified compounds led to the identification of many antimicrobial VOC, with 1-butanol and 3-methyl-acetate being most effective (Strobel 2006a; Strobel et al. 2001). However, none was lethal to the testers individually, suggesting that *Muscodor* VOC work synergistically or additively (Strobel, 2006a). Additional *M. albus* isolates and related species, some of which exhibit similar VOC-mediated antimicrobial activities, have been isolated (Strobel 2006b; Zhang et al. 2010). The potential of *M. albus* and its VOC as biofumigants for controlling plant pathogens, human pathogens, and post-harvest pathogens has been demonstrated (Mercier and Smilanick 2005; Ramin et al. 2005; Strobel et al. 2001).

Some biocontrol fungi appear to employ VOC to control pathogenic fungi (Bruce et al. 2003; Humphris et al. 2002; Hynes et al. 2007). Members of the genus *Trichoderma* have been shown to effectively parasitize or inhibit a wide range of soilborne fungal pathogens by employing multiple mechanisms, such as mycoparasitism, nutrient competition, and secretion of inhibitory compounds and hydrolytic enzymes (Harman 2011; Lorito et al. 2010). *Trichoderma viride* and *T. aureoviride* emitted VOC that inhibit the growth and protein production of *Serpula lacrymans*, a wood-rotting basidiomycete. However, *T. pseudokoningii* had no effect on any of the *Serpula* isolates tested, suggesting the species-specific nature of antifungal VOC production (Humphris et al. 2002). Similarly, the degree of growth inhibition of *F. oxysporum* f. sp. *ciceris*, a

soilborne fungal pathogen that causes chickpea wilt, by VOC produced by multiple isolates of three *Trichoderma* spp. also varied depending on the combination of the *Trichoderma* and *F. oxysporum* f. sp. *ciceris* isolates tested (Dubey et al. 2007). *F. oxysporum* strain MSA35, which enhanced lettuce growth via VOC (Minerdi et al. 2011), also produces VOC that inhibit the growth of pathogenic strains of *F. oxysporum*, and the production of these antifungal VOC requires the presence of ectosymbiotic bacteria (Minerdi et al. 2009). Although the VOC contributing to *Trichoderma* spp.'s biocontrol activity have not yet been identified, α -humulene (Fig. 2), a sesquiterpene emitted by MSA35, but not MSA35 cured of its symbiotic bacteria, was shown to inhibit mycelial growth and downregulate the expression of several virulence genes in pathogenic *F. oxysporum* strains, supporting its involvement in biocontrol (Minerdi et al. 2009).

Fungal VOC as signals mediating intra- and interspecies communications.

Some microbial VOC are utilized for dialog rather than warfare. Just as bacteria coordinate their activities in their communities via chemical signals (e.g., quorum sensing via the use of N-acyl homoserine lactone), fungi also use diverse chemical signals, some of which are volatile, to control processes critical to their ecology and reproduction such as nutrient acquisition, sporulation, spore germination, and sexual development (Bennett et al. 2013; Leeder et al. 2011). Accordingly, VOC that affect such processes control the structure and emergent properties of the microbial communities associated with plants, thus influencing the plant health and fitness both directly and indirectly. One well-known form of communication occurs when too many spores exist in proximity. Under such conditions, fungi suppress spore germination through the use of self-inhibitors (a phenomenon known as the “crowding effect”), probably to enhance the likelihood of survival and proliferation upon germination. *Penicillium paneum* employs 1-octen-3-ol (Fig. 2), a VOC commonly produced by many other fungi, to control conidial germination in a reversible manner (Chitarra et al. 2004, 2005). This VOC was shown to inhibit germ-tube formation, alter the intracellular pH, increase the permeability of the membrane, and alter protein expression (Chitarra et al. 2005). In *Trichoderma* spp., 1-octen-3-ol and its analogs 3-octanol and 3-octanone (Fig. 2) appear to participate in controlling conidiation in a concentration-dependent manner (Nemcovic et al. 2008). Conidiating colonies of *Trichoderma* spp. produced these VOC and induced conidiation in neighboring colonies even in the absence of light, a known inducer of conidiation, suggesting that certain VOC may act as fungal “hormones” and control fungal development (Leeder et al. 2011).

Many fungi rely on insects for dispersing their spores, a service critical for secondary colonization, disease development, and sexual development, and some of these fungi produce VOC mimicking those produced by flowers to attract pollinator insects (Bruce et al. 2005; Dudareva et al. 2006; Roy 1993). This mimicry also works in the opposite direction, because certain flowering plants produce VOC that mimic the scent of mushroom fruiting bodies to attract insects (Kaiser 2006). The heterothallic mating system of the grass endophytic *Epichloë* sp. relies on *Botanophila* flies for transferring gametic spores from grasses colonized by strains of the opposite mating type to stromata. Analysis of VOC produced by stromata of five *Epichloë* spp. and field bioassays using synthetic compounds led to the identification of two compounds, methyl (Z)-3-methyldodec-2-enoate (Steinebrunner et al. 2008b) and chokol K (Schiestl et al. 2006; Steinebrunner et al. 2008b) as major attractants. Both compounds elicit re-

sponses in the fly olfactory system (Steinebrunner et al. 2008b). Other fungal VOC, such as 1-3-octanol, 1-octen-3-ol, and octan-1-ol (Fig. 2), also have been shown to attract insects (Faldt et al. 1999).

Synthesis: biological and ecological roles of microbial VOC represent a mostly uncharted frontier that awaits systematic explorations.

Given the large number of VOC identified from the limited number of microbial species surveyed to date (Effmert et al. 2012; Kramer and Abraham 2012; Schulz and Dickschat 2007), we have observed only a glimpse of this chemical ecology frontier. Not only are many novel VOC and their functions waiting to be discovered but known VOC also are likely to have hitherto unrecognized biological and ecological roles, some of which may offer novel solutions for managing agricultural and environmental problems. Systematic exploration of microbes in diverse ecosystems, in combination with their phylogenetic contexts, will help us to develop hypotheses concerning the evolution, function, and ecological roles of VOC production in microbes. Microbial culture collections, especially those associated with detailed genotypic and phenotypic data, offer readily available materials for comprehensive survey of VOC in specific taxa. Resulting data not only will advance our understanding of critical ecosystem processes and services but also will assist in developing novel means for controlling agricultural and environmental problems via the use of beneficial microbes.

Multiple indicators that are associated with the composition and activity of microbial communities have been employed to study how these communities impact ecosystems and how changing environmental conditions or human activities have impacted them. McNeal and Herbert (2009) proposed the utility of VOC as potential indicators to assess the status of soil microbial communities over large spatiotemporal dynamics and environmental perturbations (McNeal and Herbert 2009). As our understanding of how various microbial VOC affect ecosystems and their constituents increases, the accuracy and value of VOC profiles as such indicators will likely improve. Versatile application of plant-derived VOC such as neem oil and *Chrysanthemum* monoterpenes in controlling pests is well established (Thacker and Train 2010). Metabolic engineering of plants or plant-associated microbes to produce VOC with fumigant activity may work as an alternative to traditional chemical control of pests. Microbial VOC-mediated growth promotion and stress resistance in plants (Farang et al. 2006; Gutierrez-Luna et al. 2010; Han et al. 2006; Kwon et al. 2010; Minerdi et al. 2009; Ryu et al. 2003, 2004; Zhang et al. 2008a,b) suggest that certain microbes and their VOC could be deployed to alleviate the heavy dependence of crop production on chemical input. The short-lived “pesticide revolution,” caused by the rapid selection and spread of pesticide-resistant insects, and the emergence of resistance to chemicals that control weeds and microbial pathogens has created a boom-and-bust cycle (Lewis et al. 1997). Plant breeding programs for disease resistance and chemical controls mostly neglect microbial partners and unknowingly may destroy this critical partnership. In order to feed the increasing world population without severely degrading the environment, we need to explore alternative or complementary solutions to current practices. Restoring or fortifying key plant-microbe partnerships would make crop plants rely less on human intervention; this strategy is particularly critical for resource-limited subsistence farming.

Several major pitfalls and challenges face researchers who seek to illuminate the roles and potential applications of microbial VOC. VOC-producing organisms emit many different compounds simultaneously, and the composition of produced VOC

is highly dynamic and likely influenced by multiple factors, such as nutrient and oxygen availability and the physiological state of the VOC producer (Insam and Seewald 2010). Accordingly, phenotypes in a tester organism may vary depending on how bacteria or fungi are cultured. Furthermore, individual VOC are likely to work synergistically or antagonistically with other VOC to affect target organisms, suggesting that, under certain experimental conditions, VOC that cause opposite effects may cancel out each other's effect and fail to cause notable phenotypes. Although evaluating identified VOC individually using their synthetic versions is a potential solution, this approach may miss VOC combinations that work synergistically. Although it probably is not practical to employ experimental designs that address all these potential pitfalls, employment of multiple well-controlled experimental conditions is critical in order not to miss too many potentially important VOC and their biological effects.

Two studies (Blom et al. 2011a; Kai and Piechulla 2009) further underscored the importance of proper experimental design and appropriate controls to accurately evaluate the role of microbial VOC in modulating plant growth and other important traits. Because increased CO₂ resulting from microbial catabolism in a closed assay system such as the I plate will enhance plant growth, negative effects of certain VOC may be masked and the degree of growth enhancement by other VOC will likely be inflated (Kai and Piechulla 2009). A survey of soil bacteria for their ability to affect the growth of *A. thaliana* revealed the critical importance of culture conditions in their VOC production (Blom et al. 2011a). Depending on the culture medium used and the inoculum density, the same strains caused opposite effects on the plants exposed to their VOC ranging from death to sixfold increase in biomass, suggesting that culture conditions significantly modulated their VOC profiles, including the type and amount of compounds (Blom et al. 2011a). This study underscores the importance of studying potential roles of microbial VOC in consideration of factors that can potentially affect VOC production.

In nature, organisms near and far are potential targets for microbial VOC, and the same VOC may perform disparate functions in many different organisms, making it difficult to choose appropriate target organisms and assay conditions for uncovering functions. However, potential clues can be found in known biological traits and ecological niches of individual microbial species and their relatives, because it is likely that the production of specific VOC is linked to the biology and ecology of individual species. For example, in discovering functions for VOC commonly produced by microbes that are closely associated with specific plants, obvious targets for evaluating their functions are host plants and other organisms associated with the host plants. The multifaceted effects of individual VOC compounds and their differential functions, depending on environmental factors and target organisms, also potentially complicate the elucidation of their roles. A good example is the common fungal volatile 1-octen-3-ol, which has been shown to affect insects (Faldt et al. 1999), plants (Kishimoto et al. 2007), and fungi (Chitarra et al. 2004). When scientists within a given subdiscipline focus on a narrow set of observable changes and potential targets, we run the risk of failing to recognize important roles and can potentially skew our view on VOC functions.

Despite these challenges, microbial VOC-mediated signaling is a potential gold mine we should explore. Model microbes and plants with rich resources and accumulated knowledge will help overcome some of the experimental challenges. As reviewed above, studies in the model plant *A. thaliana* have been instrumental in elucidating the function and mechanism of action of VOC from both bacteria and fungi. This model

plant will continue to facilitate systematic screening of diverse microbes for their ability to affect plants via VOC production and subsequent studies on underlying mechanisms, thus serving as a stepping stone for parallel studies on economically important plants. However, because *A. thaliana* may not respond to certain VOC that otherwise affect other plants, the importance of developing additional model plants cannot be overlooked. Another key consideration is balancing laboratory and field studies. Technological advances with respect to profiling and analyzing VOC; genome sequencing and functional genomics tools; and tools for studying the molecular, physiological, and cellular changes in plant and microbial systems no doubt will accelerate studies on the biosynthesis and modes of action of microbial VOC. Finally, we must remember that, despite their enormous reductionist value, such molecular approaches cannot substitute for field experiments that evaluate the roles of VOC and their producers under natural ecological settings. Advancement of our fundamental understanding as well as the development and deployment of VOC-based solutions for agricultural and environmental problems will require approaches at many levels.

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