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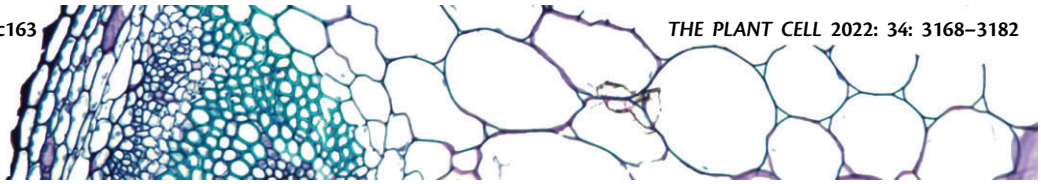

Review

Plant–microbe interactions in the rhizosphere via a circular metabolic economy

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Abstract

Chemical exchange often serves as the first step in plant–microbe interactions and exchanges of various signals, nutrients, and metabolites continue throughout the interaction. Here, we highlight the role of metabolite exchanges and metabolic crosstalk in the microbiome–root–shoot–environment nexus. Roots secret a diverse set of metabolites; this assortment of root exudates, including secondary metabolites such as benzoxazinoids, coumarins, flavonoids, indolic compounds, and terpenes, shapes the rhizosphere microbiome. In turn, the rhizosphere microbiome affects plant growth and defense. These inter-kingdom chemical interactions are based on a metabolic circular economy, a seemingly wasteless system in which rhizosphere members exchange (i.e. consume, reuse, and redesign) metabolites. This review also describes the recently discovered phenomenon "Systemically Induced Root Exudation of Metabolites" in which the rhizosphere microbiome governs plant metabolism by inducing systemic responses that shift the metabolic profiles of root exudates. Metabolic exchange in the rhizosphere is based on chemical gradients that form specific microhabitats for microbial colonization and we describe recently developed high-resolution methods to study chemical interactions in the rhizosphere. Finally, we propose an action plan to advance the metabolic circular economy in the rhizosphere for sustainable solutions to the cumulative degradation of soil health in agricultural lands.

Introduction

Over millions of years, plants and microbes have developed various associations ranging from mutualistic to parasitic. Plants and their associated microbes can be considered holobionts, in which the host relies on its microbiome for specific functions and traits (Rosenberg et al., 2009). It is estimated that the number of microbial cells colonizing plants is higher than the sum of plant cells, particularly those colonizing the root (Mendes et al., 2013). The rhizosphere is considered the richest source of organic material in soil and therefore a hotspot for microbial growth and activity (Reinhold-Hurek et al., 2015). Moreover, the number of microbes in the rhizosphere (soil around the root zone) is 5–10 times higher than in nonrhizospheric soil (Groleau-Renaud et al., 2000). The rhizosphere microbiome provides diverse benefits to its plant host: microbes promote plant growth (Lugtenberg and Kamilova, 2009), support nutrient uptake (Weidner et al., 2015), improve tolerance to abiotic

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stress (Yang et al., 2009), defend the plant host against pathogens (Raaijmakers et al., 2009; Shi et al., 2017), and modulate the plant immune system to induce resistance (Bakker et al., 2013).

Roots select specific microbial populations and shape the microbiome composition in their vicinity (i.e. the rhizosphere) and internal tissues (i.e. the endosphere) (Bulgarelli et al., 2012; Bai et al., 2015; Uroz et al., 2019). To date, an exceptional number of reports have provided ample information regarding bacterial community structure in the rhizosphere of different plant species (mostly model and crop plants, but also some wild species) (Bai et al., 2015; Bulgarelli et al., 2015; Kawasaki et al., 2016). Although less well-studied than bacteria, fungal communities in the rhizosphere have also been systematically described (Berlanas et al., 2019). Archaea, oomycetes, protozoa, and viruses are also found in the rhizosphere (Mendes et al., 2013).

Chemical exchanges play an important role in the complex interactions among members of the root microbiome. Much of the research reporting the effect of root exudates on rhizosphere microbes was performed on dual relationships, such as plant interactions with nitrogen-fixing bacteria, mycorrhizal fungi, plant growth-promoting rhizobacteria, biocontrol microorganisms, and with pathogenic fungi and bacteria (Table 1). Understanding the chemodiversity and the chemical signaling affecting root activity and/or shaping rhizosphere microbial activity is hence pivotal to protect plants in nature and improve crop productivity.

Root growth, metabolism, and exudation are crucial for establishing interactions with rhizosphere microbiota. Root exudation is the main source of organic compounds released into the rhizosphere. Changes in soil parameters caused by root activity, known as soil conditioning, affect plant–soil feedback (Herrera Paredes and Lebeis, 2016). Soil conditioning has a major effect on microbial growth and activity in the rhizosphere. Conversely, rhizosphere microorganisms influence plant metabolism and performance (Korenblum and Aharoni, 2019). Microbial modulation of plant metabolism can be local or systemic; known systemic responses induced by microbial colonization of roots include: (1) nitrogen fixation (i.e. autoregulation of nodulation [AON]; [Reid et al., 2011]), (2) disease resistance (i.e. induced systemic resistance [Pieterse et al., 2014]) and, recently, (3) root exudation can be microbially modulated through a systemic response (i.e. SIREM for "Systemically Induced Root Exudation of Metabolites" [Korenblum et al., 2020]).

This review focuses on the chemical interaction between rhizosphere microbes and plant roots, including processes that modulate plant metabolism. We present a critical appraisal of plant root exudation and its effect on rhizosphere microbes, and compare the effect of conditioned and non-conditioned soils on the rhizosphere microbiome composition of the next generation of plant host (aka microbiome soil borne legacy) (Bakker et al., 2018). Root exudates shape the rhizosphere microbiome, which influences plant metabolism and exudation (as in SIREM). Finally, we bring a suit of evidence for host–microbiome and metabolome crosstalk, that is, plants eavesdrop on chemical communication between microbes, and vice-versa. Bringing these data together, it follows that the microbiome–root–shoot–environment nexus (Hou et al., 2021b, 2021a) is based on what can be delineated as "metabolic circular economy" (Figure 1) influencing rhizosphere interactions and plant health.

Carbon sinks in the rhizosphere

Carbon allocation is vital for plants to adapt to environmental changes. The trade-off between carbon sink and source activities will finally govern the success of plant growth (Lemoine et al., 2013), but also has a major impact on plant interactions with its microbiota (Hennion et al., 2019). Consequently, belowground carbon allocation reflects a wide range of physiological and ecological strategies, such as nutrient mobilization (e.g. iron acquisition) and selecting the rhizosphere microbiome through root exudation. Plants exude large amounts of substances made of photosynthetically fixed carbon through the roots into the rhizosphere, the zone of soil under the immediate influence of plant roots (Hiltner, 1904). Root exudates contain a wide variety of small molecules including amino acids, carbohydrates, organic acids, hormones, vitamins, and different classes of specialized metabolites (Venturi and Keel, 2016; Sasse et al., 2018). Metabolite patterns and quantity of root exudates are dependent on plant species, age, and environment (Maurer et al., 2021).

Root exudation requires the transport of molecules to the root system from the shoot and/or through root cell layers and subsequent release to soil. We currently have little understanding of how metabolite secretion ensues and its associated regulatory mechanisms. To be secreted by cells of the epidermis and possibly by root cap cells, a molecule needs to traverse the plasma membrane and permeate the cell wall. Thus, membrane transporters are likely involved in root chemical secretion. Exudation of primary metabolites (e.g. sugars and amino acids) is facilitated by transporters (e.g. SWEET transporters) along the concentration gradient (Breia et al., 2021). As most secondary metabolites cannot simply diffuse through membranes, especially metabolites that are modified by glycosylation, acylation, or hydroxylation, the secretion of these molecules is likely an active process. In one of only a few examples, export of coumarins from roots in *Arabidopsis thaliana* is mediated by a Pleiotropic Drug Resistance (PDR)-Type ATP-Binding Cassette (ABC) transporter (ABCG37/PDR9; Ziegler et al., 2017). ABCG37/PDR9 was also associated with transport of the endogenous auxin precursor indole-3-butyric acid in Arabidopsis signifying a most likely promiscuous activity of such proteins (Růžička et al., 2010). Apart from the limited number of transporters associated with metabolite exudation (Weston et al., 2012; Sasse et al., 2018; Canarini et al., 2019) we also have a major gap of knowledge with respect

Table 1 Overview of studies reporting the effect of root exudates from different plant species on various rhizosphere microbes

Plant species	Metabolite/whole exudate	Effect (±)	Rhizosphere microorganism	Reference
Alfalfa (*M. sativa*)	7,4′-Dihydroxyflavone and naringenin	+	Acidobacteria	Szoboszlay et al. (2016)
Arabidopsis (*A. thaliana*)	Phytochemical extracts from root exudates	+	Microbiome	Badri et al. (2013)
Arabidopsis	Malic acid	+	*B. subtilis* FB17	Rudrappa et al. (2008)
Arabidopsis	Scopoletin	−	*F. oxysporum* and *V. dahliae*	Stringlis et al. (2018)
Arabidopsis	Sideretin and fraxetin	−	*Pseudomonas* sp. Root329	Voges et al. (2019)
Arabidopsis	Thalianin, thalianyl fatty acid esters, and arabidin	+	Proteobacteria	Huang et al. (2019)
		−	Actinobacteria	
Arabidopsis	Camalexin	+	*Pseudomonas* sp. CH267	Koprivova et al. (2019)
Arabidopsis and alfalfa	Whole exudate effect	±	Fungal community	Broeckling et al. (2008)
Arabidopsis *abcg30* mutant	Whole exudate effect	+	Microbiome analysis (e.g. *Bradyrhizobium*)	Badri et al. (2009)
Arabidopsis *myc2* and *med25* mutants	Whole exudate effect	+	Microbiome analysis (*Streptomyces*, *Bacillus*, and *Lysinibacillus*)	Carvalhais et al. (2015)
Banana (*Musa acuminata*)	Malic and fumaric acids	+	*B. amyloliquefaciens* NJN-6	Yuan et al. (2015)
Chinese tallow (*Triadica sebifera*)	Flavonoid	+	AM fungi	Tian et al. (2021)
Eucalyptus globulus ssp. *Bicostata*	Rutin	+	*Pisolithus*	Lagrange et al. (2001)
Common bean (*Phaseolus vulgaris*)	Flavonoid	+	*Rhizobium leguminosarum*	Aguilar et al. (1988)
Maize (*Z. mays*)	Benzoxazinoids	−	Flavobacteriaceae and Comamonadaceae	Cadot et al. (2021)
Maize	2,4-Dihydroxy-7-methoxy-2H-1,4-benzoxazin-3(4H)-one	+	*P. putida* KT2440	Neal et al. (2012)
Maize	(6R)-7,8-Dihydro- 3-oxo-ionone and (6R; 9R)-7,8-dihydro-3-oxo-ionol	−	*F. oxysporum* f. sp. *melongenae*	Park et al. (2004)
Maize	Flavones	+	Oxalobacteraceae	Yu et al. (2021)
Maize	Whole exudate effect	+	*B. amyloliquefaciens* SQR9	Zhang et al. (2015)
Peanut (*Arachis hypogaea*)	Alanine and other amino acids	+	*F. oxysporum* and *F. solani*	Li et al. (2013)
Pine (*Pinus radiata*)	Quinic, lactic, maleic acids	+	Microbiome	Shi et al. (2011)
Potato (*Solanum tuberosum*)	Tyramine and other amino acids	+	*S. subterranean*	Balendres et al. (2016)
Sand Sedge (*Carex arenaria*)	Volatile	+	Soil bacteria	Schulz-Bohm et al. (2018)
Sugarbeet (*Beta vulgaris*)	Whole exudate effect	+	*P. aeruginosa* PA01	Mark et al. (2005)
Tobacco	Whole exudate effect	+	*Paenibacillus elgii*	Das et al. (2010)
Tomato (*S. lycopersicum*)	α-Tomatine	+	Sphingomonadaceae	Nakayasu et al. (2021)
Tomato	Whole exudate effect	+	*F. oxysporum* f. sp. *lycopersici*	Scheffknecht et al. (2006)
Tomato	Whole exudate effect	+	*Pseudomonas* spp.	Kravchenko et al. (2003)
Tomato and cucumber (*Cucumis sativus*)	Citric acid	+	*Pseudomonas fluorescens* PCL1751, *P. fluorescens* PCL1753, *Pantoea agglomerans* PCA0067, and *Aeromonas hydrophila* PCA0081	Kamilova et al. (2006)
Watermelon (*Citrullus lanatus*)	Chlorogenic acid	−	*F. oxysporum* f. sp. *niveum*	Ling et al. (2013)
Watermelon	Cinnamic acid	+	*F. oxysporum* f. sp. *niveum*	Ling et al. (2011)
Wild oat (*Avena barbata*)	Organic acids nicotinic, shikimic, salicylic, cinnamic and IAA	+	*Microbacterium* HA36, *Flavobacterium* HB58 and *Cellulomonas* HD24	Zhalnina et al. (2018)

to the precise location of root metabolite accumulation and the exact location of exudation. In recent work, we employed matrix-assisted Mass Spectrometry Imaging (MSI) and demonstrated the spatial localization of secondary metabolites in tomato (*Solanum lycopersicum*) roots (Korenblum et al., 2020). Some metabolites were specifically found on the tips of lateral roots (e.g. the acylsugar S1:5), while other metabolites were only detected on the hairs of

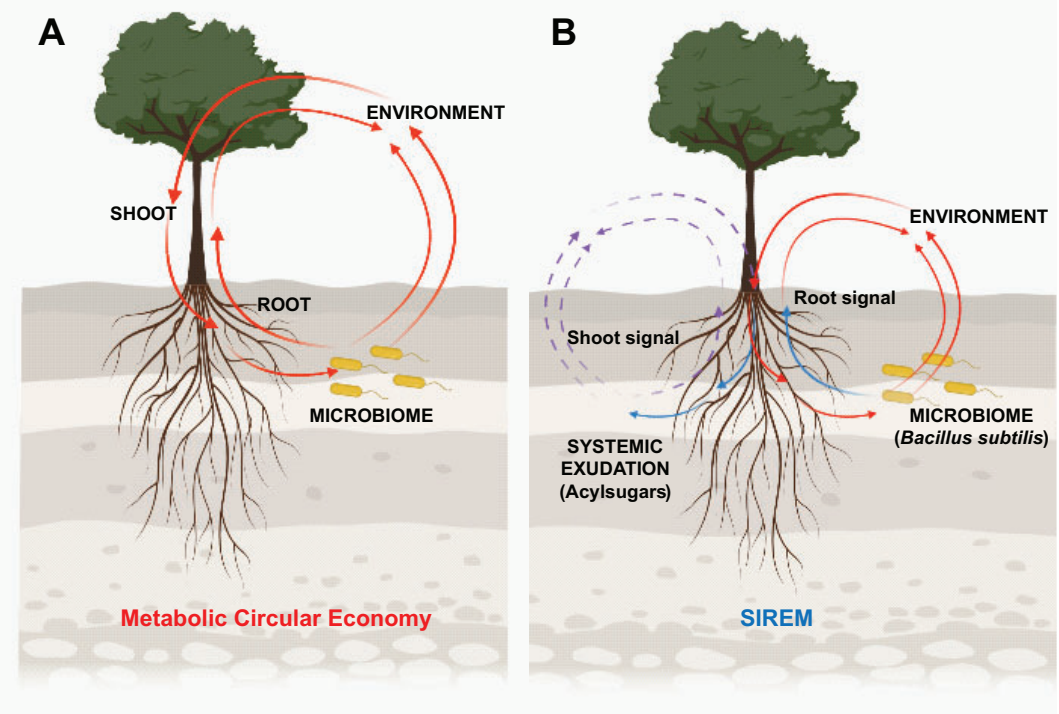

Figure 1 Metabolic circular economy in the rhizosphere. A, Schematic representation of chemical allocation in the phytobiome. The microbiome–root–shoot–environment nexus is based on a metabolic circular economy that influences rhizosphere interactions where metabolites are exchanged (i.e. consumed, reused and redecorated [redesigned]) by different rhizosphere microbiome members. B, SIREM leads to shifts in the chemical diversity in the rhizosphere and is microbiome-driven. SIREM (blue arrows) is a mechanism of the metabolic circular economy system (red and purple arrows). SIREM-related acylsugar exudation is induced by the soil bacterium *B. subtilis*.

the main root (e.g. acylsugar S4:19 and hydroxytomatine). MSI was also used in a different study to reveal the spatial distribution of metabolites involved in regulating biological nitrogen fixation within soybean root nodules (Veličković et al., 2018). An alternative to MSI techniques to track the precise location of metabolite accumulation in roots is the use of a biosensor. Pini et al. (2017), employed *Rhizobium* bio-reporter strains to map root secretion of sugars, polyols, amino acids, organic acids, or flavonoids in pea (*Pisum sativum*) roots and nodules. In pea nodules, dicarboxylates and sucrose are the main carbon sources. This evidence suggests that root exudation is likely variable along the root axis.

As early as 1904, Hiltner noted the selection of a unique population of microorganisms by the chemicals released from plant roots (Hiltner, 1904). Since then, a relatively small number of specific plant metabolites have been described to impact the root microbiome and several studies have tested the effect of total root exudates collections on soil microorganisms. Here, we provide a comprehensive list of studies that evaluated the effect of root exudates on the rhizosphere microbes, including plant volatiles (Table 1). Whole exudate collections are typically composed of a wide range of molecules, including high and low molecular weight compounds affecting both bacterial and fungi soil microorganisms. Arabidopsis and alfalfa (*Medicago sativa*) whole exudate extracts exhibit a plant-specific effect on soil fungal communities (Broeckling et al., 2008), while genetic modification of active metabolite transporters (Badri et al., 2009) or key regulators of pathogen defense genes (Carvalhais et al., 2015) resulted in changes of root exudates composition and microbial communities.

Metabolites exuded through the roots are either synthesized in the roots or supplied by the shoot. Roots are supplied with sugars that were synthesized in the leaves and are mostly used for maintenance of root growth during early growth stages (Hennion et al., 2019). Correspondingly, in Arabidopsis, sugars are exuded by roots in the greatest abundance early in the plant's life cycle (7–10 days old) (Chaparro et al., 2014); in later stages (18–21 days old), sugars are still found in root exudates and have some contribution to the Arabidopsis rhizosphere microbiome structure (Badri et al., 2013). The rhizosphere effect of organic acids exuded from plant roots has been frequently studied (Kamilova et al., 2006; Rudrappa et al., 2008; Ling et al., 2011, 2013; Shi et al., 2011; Zhalnina et al., 2018). Apparently, rhizosphere bacteria grow preferentially on aromatic organic acids exuded by plants (i.e. malonic, malic, nicotinic, shikimic, salicylic, cinnamic, and indole-3-acetic acids) (Oburger et al., 2009; Zhalnina et al., 2018). Being one of the most labile carbon sources in the rhizosphere, when released by roots organic acids are quickly consumed (i.e. uptaken or biodegraded) by the rhizosphere microbiota (Oburger et al., 2009). These studies provided evidence that the chemical composition of root exudates, the substrate

preference, and competition of soil microbes determine the structure and function of the rhizosphere microbiome. Soil conditioning through exudation of organic acids regulates the composition of the rhizosphere microbiome and apparently promotes the growth of microbes that assist plants fitness. For instance, malic and fumaric acids released by banana roots are crucial for *Bacillus amyloliquefaciens* NJN-6 colonization on the host roots. *Bacillus amyloliquefaciens* NJN-6, originally isolated from the rhizosphere of banana plants, was shown to protect these plants from *Fusarium oxysporum* f. sp. *cubense* and promote their growth (Yuan et al., 2015). Interestingly, organic acid treatment of soil was shown to improve soil physicochemical performance and affect the structure of the soil microbial community (by inducing the enrichment of plant growth-promoting bacteria). Following these findings, the authors suggested the use of organic acids as soil prebiotics (Macias-Benitez et al., 2020). Conversely, amino acids were associated with enhanced growth of pathogenic microorganisms. A typical example is the production of tyramine and other amino acids by potato roots, leading to *Spongospora subterranea* growth, a major crop-threatening pathogen (Balendres et al., 2016). Alanine and other amino acids secreted from peanuts were also found to promote the growth of *F. oxysporum* and *Fusarium solani* (Li et al., 2013). Amino acids in the rhizosphere may serve as sources of both carbon and nitrogen; while microbes seemingly prefer to uptake inorganic nitrogen, the ability to take up amino acids confers an advantage by some opportunistic soil pathogens (Moe, 2013).

The role of plant secondary metabolites in rhizosphere interactions

Besides organic acids and sugars that are essential carbon sources, secondary metabolites can also shape the rhizosphere microbiome. They function as semiochemicals mediating interactions or as toxic compounds deterring plant pathogens. For instance, flavonoids are hitherto one of the most studied chemical classes in root exudates. The various branches of the intricate flavonoid pathway exhibit diverse effects on soil microorganisms (Hassan and Mathesius, 2012; Weston and Mathesius, 2013). They are pivotal in attracting rhizobia to the root system of legume plants and induce nodule formation by activation of *nod* genes from the rhizobia. Legume-nodulating rhizobia use quorum-sensing (QS) *N*-acyl homoserine lactones (AHLs) to regulate this symbiotic interaction and flavonoids (e.g. genistein, apigenin, and daidzein) can also increase the production of autoinducers and consequently the expression of AHL synthesis genes in rhizobia (Pérez-Montaño et al., 2011). Conversely, certain flavonoids inhibit QS in *Pseudomonas aeruginosa* and *Escherichia coli* through allosteric inhibition of receptors (Paczkowski et al., 2017; Manner and Fallarero, 2018). Root excreted flavonoids are also well-known for inducing the establishment of arbuscular mycorrhizal (AM) symbiosis (Tian et al., 2021) and as defense molecules against soil-borne pathogens. Interestingly, the Nod Factors from *Bradyrhizobium* and *Rhizobium* were shown to induce exudation of flavonoids in higher amounts in soybean (*Glycine max*) plants (Schmidt et al., 1994). Maize (*Zea mays*) roots exude metabolites from different chemical classes, mostly benzoxazinoids (see below) and flavonoids are secreted into the rhizosphere. The flavone apigenin exuded by maize roots was shown to affect plant growth and nitrogen nutrition by a microbial-driven process, that is, oxalobacteraceae is enriched in apigenin-containing rhizosphere and promote plant growth and nitrogen acquisition (Yu et al., 2021).

Another milestone in rhizosphere chemistry was the recent discovery that coumarins shape the Arabidopsis root microbiome when grown under low iron conditions (Stringlis et al., 2018; Voges, et al., 2019). Specifically, scopoletin inhibits the growth of two soil-borne fungal pathogens, *F. oxysporum* and *Verticillium dahlia* (Stringlis et al., 2018). While catecholic coumarins (e.g. fraxetin) inhibit the growth of the bacterial strain *Pseudomonas* sp. Root329, these molecules could improve *Bacillus subtilis* biofilm formation (Figure 2). *Bacillus subtilis* is widely used in agriculture as a biocontrol agent against various plant pathogens. Root colonization is dependent on its ability to form biofilm on roots and requires active iron acquisition from the soil milieu by producing catecholic siderophores (Chen et al., 2012; Rizzi et al., 2019). While *B. subtilis* likely uses the plant-derived catecholic coumarins as iron chelators; the proposed mode of action of these molecules against *Pseudomonas* involves the generation of reactive oxygen species (Voges et al., 2019). Besides flavonoids and coumarins, different phenylpropanoids can be secreted from watermelon roots and showed an opposite effect on the same soil microorganisms. Ling et al. (2013) showed that chlorogenic acid from watermelon has a negative effect on the pathogen *F. oxysporum* f. sp. *niveum*, while the upstream compound in the phenylpropanoid pathway, cinnamic acid, was found to support the growth of the same fungi (Ling et al., 2011).

Arabidopsis root-derived triterpenes also exert a dual effect on the root microbiome. A blend of specific root-derived triterpenes (namely thalianin, thalianyl medium-chain fatty acid esters, and arabidin) in Arabidopsis, may increase the proliferation of bacterial strains belonging to Proteobacteria strains while it inhibits the growth of Actinobacteria strains. Terpenes are the largest group of plant secondary metabolites showing a vast diversity of chemistries (Chen et al., 2004; Huang and Osbourn, 2019; Muchlinski et al., 2019). This class of metabolites likely confers a broad spectrum of biological activities in the rhizosphere; yet no molecular mechanism of action of root-derived terpenes on rhizosphere bacteria was disclosed. Nevertheless, monoterpenes are known to exhibit antibacterial activity, for example, carvacrol and thymol disturb membrane integrity of nonplant associated bacteria (Solórzano-Santos and Miranda-Novales, 2012). The sesquiterpene lactone strigolactone, which was first identified in root exudates of cotton plants a few decades ago (Cook

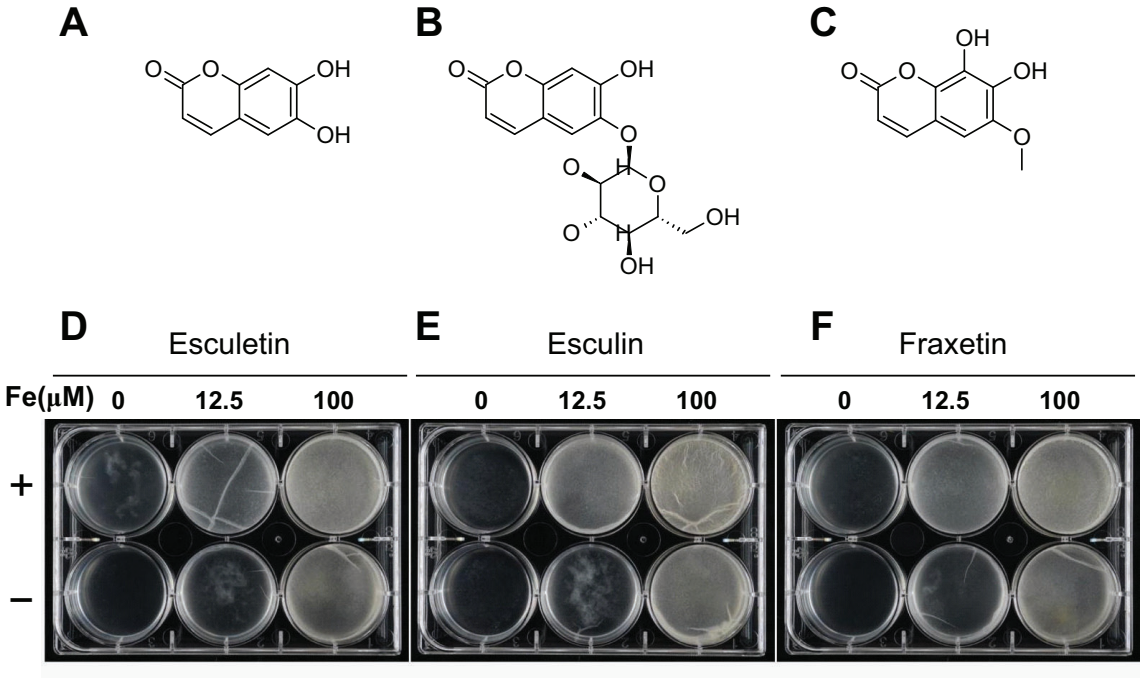

Figure 2 Coumarins from Arabidopsis root exudate improve biofilm formation of the soil bacterium *B. subtilis*. Structures of the coumarins Esculetin (A), Esculin (B), and Fraxetin (C) are depicted. The effect of these molecules (D, E, and F, respectively) in a *B. subtilis* pellicle assay conducted with a final concentration of 5 μM of each coumarin is shown. The sign (+) on the left side indicates coumarin treatment and the (–) sign indicates control (without coumarin). Bacterial cells were inoculated into the growth medium with different iron concentrations, and incubated at 23°C for 2 days in dark before imaging. Biofilm formation appears as a bright layer in the positive wells. In low iron condition, root-derived coumarins improve *B. subtilis* biofilm formation.

et al., 1966), influences AM symbiosis and rhizobial root interactions (López-Ráez et al., 2017). In rhizobial interactions, strigolactones affect swarming motility of the rhizobacteria. In AM symbiosis, strigolactones are exuded into the rhizosphere and attract AM fungi; in return, the fungal counterpart provides phosphate and facilitates plant water uptake. Several strigolactones were isolated and associated to the induction of hyphal branching in AM fungi (AMF), which is a critical step in host recognition; for instance 5-deoxystrigol in *Lotus japonicus* (Akiyama et al., 2005), orobanchol and solanacol in tomato plants (López-Ráez et al., 2008). For additional details on the role of strigolactones in plant interactions with beneficial and detrimental organisms, see for example the review by López-Ráez et al. (2017).

The localization of biosynthesis of indole-derived specialized metabolites, such as camalexin and benzoxazinoids, is critical to root exudation and interactions. Arabidopsis and other *Brassicaceae* plants produce and secrete camalexin in the shoot and in the root as a phytoalexin against pathogens. Interestingly, root-specific biosynthesis of camalexin that is dependent on the activity of the cytochrome P450 CYP71A27 in Arabidopsis, is pivotal to the plant interactions with multiple microbial strains (Koprivova et al., 2019). A remarkable association of the activity of CYP71A27 in roots and the sulfatase activity in bacteria appeared crucial to plant growth promotion by *Pseudomonas* sp. CH267 and MPI9 strains. Pharmacologically effective doses of camalexin complemented both effects of the CYP71A27 gene knockout, the sulfatase activity, and the plant growth promotion by *Pseudomonas* sp. CH267. The plant defense benzoxazinoids (BX), specifically the aglycones 2,4-dihydroxy-1,4-benzoxazin-3-one and 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one glucoside, are predominantly secreted from crown roots (roots originating from the stem) as compared to primary roots (roots developing from the radicle). The rhizosphere microbial community structure from BX-producing wild-type maize differs from that of a BX-deficient *bx1* mutant of maize (Hu et al., 2018), and crown root-associated communities of both wild-type and BX-deficient mutants show reduced diversity indices when compared with primary root-associated communities (Cotton et al., 2019). Mutant lines have been used to identify the role of BX and other plant metabolites in rhizosphere interactions, but those specific metabolic changes in mutant lines may affect overall plant metabolome and consequently change the metabolic pattern of the root exudates. For instance, Cotton et al. (2019) showed that benzoxazinoids deficient *bx1* and *bx2* mutants of maize influence the rhizosphere microbiome by an endogenous regulatory activity on a wider spectrum of plant-derived rhizosphere signals (e.g. flavonoids). This key observation highlights a challenge in deciphering the role of secondary metabolites in the rhizosphere; metabolic engineering primarily targets one metabolite or gene but it usually generates off-target metabolic changes (Lv et al., 2014). Plant metabolism is highly intertwined and perturbation of a single gene leads to multiple

consequences on metabolic flux. Thus, besides complementation assays, as used in the case of camalexin by Koprivova et al. (2019), a system-wide analysis might be assisting in evaluating the whole exudate effect on the root microbiome.

Plant–soil feedback and root–shoot–root systemic responses

By changing soil properties, root exudation has a fundamental role in plant–soil feedbacks also in further generation of plants, the so-called microbiome driven "soil-borne legacy" (Bakker et al., 2018). The best-studied case of the benefits of soil conditioning on new generations growing in the same soil is the agricultural phenomenon of disease-suppressive soils. Improved suppression of fungal and bacterial plant pathogens is associated with the enrichment of antagonistic microbial members in the soil microbiome. Examples include the take-all disease of wheat (*Triticum aestivum*) (Berendsen et al., 2012), scab disease of potato (Sagova-Mareckova et al., 2015) and black rot disease of tobacco (*Nicotiana tabacum*) (Almario et al., 2014). In maize, benzoxazinoids recruit rhizosphere bacteria (e.g. the plant beneficial bacterium *Pseudomonas putida*) that enhance jasmonate signaling and defense responses in the next generation of plants (Hu et al., 2018). While soil conditioning functions in assembling a more health-promoting root microbiota, benzoxazinoids secretion also enriches various potential plant pathogenic fungi (Cadot et al., 2021). Some soils are naturally suppressive, but disease suppression can also be determined by the plant host selection of antibiotic producing bacteria from the native soil microbiota. For instance, a specific tomato variety (Hawaii 7996) recruits a rhizospheric flavobacterium against the soil-borne pathogen *Ralstonia solanacearum* and rhizosphere transplantation of this resistant plant transfers the ability to control disease symptoms in a susceptible tomato variety (Kwak et al., 2018). Specific root exudation pattern likely results in the recruitment of this flavobacterium by resistant plants. In Arabidopsis, alteration of root exudation patterns and increased resistance to *Pseudomonas syringae* were observed in plants grown in conditioned soils (i.e. soils used to grow multiple plant generations that were infected by *P. syringae*) (Yuan et al., 2018). Infected plants exuded through the roots increased amounts of amino acids and long-chain organic acids. The addition of these molecules into the rhizosphere was found to elicit disease suppression.

Microbial-driven changes in root metabolite profiles, gene expression and developmental patterns were reported numerous times. SIREM (Korenblum et al., 2020) is a root–root long-distance signaling mediated by the root microbiome. In SIREM, tomato rhizosphere microbiome modulates the chemical diversity secreted to the rhizosphere by changing the patterns of root exudation through a systemic root–shoot-root signaling mechanism. Using a split-root hydroponic system, different soil microbiomes introduced to one root side ("local side") were used to evaluate the effect of the root microbiomes on the metabolites secreted in the second root side ("systemic side"; kept under axenic conditions). Three root microbiome treatments were prepared with high, medium, and low microbial diversity levels (termed HD, MD, and LD, respectively). Following 7 days of root microbiome treatment, metabolic profiling of root exudates in the "systemic side" revealed that 53.3%–75.4% of the total mass features (detected in electrospray negative or positive ionization mode, respectively) were significantly modulated by one of the three microbiome treatments. We detected a total of 115 metabolites that were significantly enriched or depleted in the systemic side that was modulated by the "local side" root microbiome. SIREM-induced metabolites represented different chemical classes including aliphatic and aromatic alcohol glycosides, fatty acids, hydroxycinnamic acid conjugates, organic acid derivatives, sulfur-containing compounds, steroidal glycoalkaloids (SGAs), steroidal saponins, and acylsugars. The latter class of metabolites is known to be produced by foliar glandular trichomes of tomato and other members of the Solanaceae family (Figure 3). These molecules consist of either glucose or sucrose backbones esterified with three to four acyl chains, each containing 2–12 carbons. In SIREM, acylsucroses (26 metabolites) and acylglucoses (G2:12 [6, 6]; seven isomers) were exuded by the "systemic side" of tomato roots; the sugar moiety and the length of the acyl chains differed according to the root microbiome composition. HD-treated plants mostly exuded acylsugars that are uniquely secreted in the course of SIREM in tomato; acylsucroses with C5 acyl chains (S1:5, S2:10, and S3:15). As in the case of acylsugars, hydroxycinnamic acid amides conjugated to tyramine or octopamine, were reported for the first time to be secreted by roots. While acylsugars and hydroxycinnamic acid conjugates were induced in HD-treated plants, ferulic acid glycosides were suppressed in LD-treated plant exudates. Tomato SGAs commonly found in tomato fruits were also SIREM-modulated in roots, such as hydroxytomatine, dehydrotomatine, and α-tomatine (Korenblum et al., 2020). Interestingly, α-tomatine was recently associated with enrichment of Sphingomonadaceae in the tomato rhizosphere, suggesting its role in belowground chemical communication (Nakayasu et al., 2021).

Another SIREM-related molecule that was detected in exudates of microbiome-treated plants was azelaic acid (AzA). It accumulated in the "systemic side" root tissue in a glycosylated form. The AzA aglycone is commonly found in leaves of various plants after pathogen attack (Lim et al., 2017); neither the aglycone nor the glycosylated form were reported previously to occur in roots nor in exudates. Following the challenge of split-root plants with AzA only, AzA was detected in systemic parts of the split-root plants, both shoot and root, in its glycosylated form (i.e. AzA-hexose). The AzA aglycone is exuded through the "systemic side" root. Additionally, AzA treatment induces systemic exudation of other metabolites, for example, the SGA

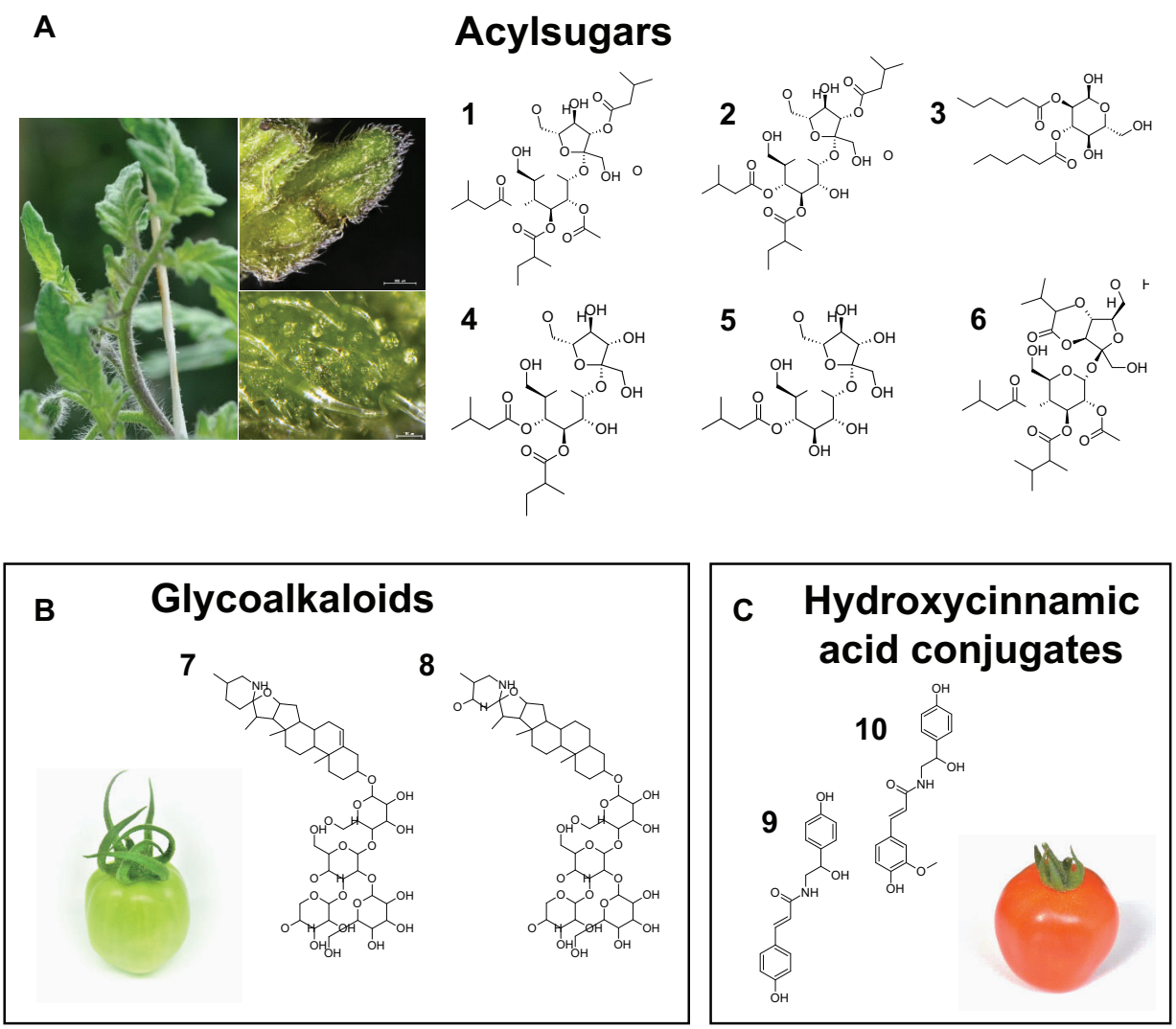

Figure 3 Root exudate chemical diversity modulated by rhizosphere microbiome. SIREM-related metabolites that are exuded from "systemic side" roots of tomato plants, which were previously detected in other tomato tissues, depicted in (A), tomato trichomes; B, unripe fruit and; C, ripe fruit. Structures of SIREM-related metabolites: A, acylsugars; B, glycoalkaloids; and C, hydroxycinnamic acid conjugates are presented. (1) S4:17 (2,5,5,5); (2) S3:15 (5,5,5); (3) G2:12 (6,6); (4) S2:10 (5,5); (5) S1:5; (6) S4:19 (2,5,6,6); (7) dehydrotomatine; (8) hydroxytomatine; (9) coumaroyloctopamine; and (10) feruloyloctopamine. The acyl chains positions were not unambiguously confirmed in the acylsugar structures and were assigned arbitrarily.

α-tomatine was higher in exudates of AzA-treated plants as compared to untreated plants (Korenblum et al., 2020).

SIREM is dependent on the colonization of roots by specific bacteria and possibly on the interaction of plant roots with other soil microbes. For instance, *B. subtilis* induced the exudation of specific tetraacylsucroses and bacteria belonging to the order Pseudomonadales were correlated to the systemic exudation of ferulic acid glycosides. Therefore, SIREM represents a microbial-driven systemic root exudation mechanism that likely promotes soil conditioning. We also suggested that AzA or AzA-hexose are SIREM-inducing molecules that might be reprograming plant metabolism. The detection of specific chemistries (with large structural diversity) in root exudates modulated by root microbiome suggests exclusive rhizosphere functions, likely important to interactions belowground. Future research is required to elucidate acylsugars' biosynthesis in roots of Solanaceae plants and unravel the specific role of these metabolites exudation in belowground interactions. Moreover, AzA biosynthesis and transport in planta also requires further research.

Plant systemic signaling mechanisms that regulate soil microbiome–root–shoot–root interactions remain little investigated to date. One challenge in such experiments is the isolation of the "local side" root from the "systemic side" root. The "split-root" experimental system is an excellent tool to reveal systemic signaling controlling root interactions with the rhizosphere microbiome (Kassaw and Frugoli, 2012; Larrainzar et al., 2014). The AON pathway is part of legume root–rhizobium symbiosis, in which nodule number is controlled by a systemic mechanism (Pervent et al., 2021). When soil N is limiting, legume plants are triggered to exude flavonoids (e.g. luteolin and apigenin), which recruit rhizobia

to the roots and induce nodule formation (Weston and Mathesius, 2013). In the nodules, the enzyme nitrogenase catalyzes the reduction of N_2 to $NH4^+$. Bacterial infection and nodule formation are controlled by nitrate availability to roots. Notably, the number of nodules is systemically regulated through a signal that is produced in the nodule/root tissue (small peptides of the CLAVATA3 /EMBRYO SURROUNDING REGION-RELATED (CLE) family [Mortier et al., 2012]). The peptides are transported to the shoot, and then a shoot-derived secondary signal is transmitted back to roots to inhibit further nodulation in distal parts of the root system. This intricate long-distance relay of small peptides (including microRNAs and hormones; Okuma et al., 2020) that is crucial for balancing between susceptibility to rhizobia colonization (i.e. nodule formation and influx of nitrogen) and the efflux of carbon compounds derived from photosynthesis to maintain the nodule active. Interestingly, autoregulation of symbiosis has also been reported for the AMF root colonization, a "common symbiosis pathway" that controls the establishment of both root nodulation and the AMF–plant symbiosis (Ikeda et al., 2010). Nodulation systemically influences AMF root colonization and the other way around (Catford et al., 2003). In AMF–plant symbiosis, CLE peptides are also produced by the fungal counterpart, which positively regulates symbiosis (Le Marquer et al., 2019).

Metabolic crosstalk in the rhizosphere

While there is no evidence of a universal language in the rhizosphere, it is clear that extensive chemical communication occurs between plants and its microbiome. The plant host and its microbiome coexisted and coevolved for millions of years. During this period of time both counterparts have been exposed to numerous chemicals, among them signaling molecules, produced and released by the other. Therefore, plants enhance and interfere with bacterial communication systems and similarly bacterial signal molecules can influence plant metabolism. Aside from modulation of metabolism, crosstalk (or "hijacking") of inter-kingdom signals (such as bacterial auto-inducers and host plant hormones) has broad implications for bacterial colonization on roots and plant fitness.

The inoculation of crops with beneficial microbes has been long explored to improve plant yield (Sessitsch et al., 2018). Several studies showed the effect of plant growth-promoting rhizobacteria on plant growth is based on their ability to produce phytohormones such as gibberellins (GAs), auxins, cytokinins (CKs), ethylene, and abscisic acid (ABA) (Freebairn and Buddenhagen, 1964; Morrone et al., 2009; Kudoyarova et al., 2014; Shahzad et al., 2017; Keswani et al., 2020). GAs were first discovered in the fungal rice pathogen *Gibberella fujikuroi*, but they are also produced by other fungi and bacteria (Salazar-Cerezo et al., 2018). Active GAs (i.e. GA_1, GA_3, GA_4, and GA_7) are pivotal for plant growth and its interaction with microbes. GA biosynthesis was unraveled recently in rhizobia, which independently evolved a biosynthetic pathway divergent from the plant and fungal ones (Nett et al., 2017). *Bradyrhizobium diazoefficiens* and other rhizobia contain an operon encoding the enzymes to produce GA. While two rhizobial diterpene cyclases (CPS and KS) share some homology with the plant and fungal cyclases, the other enzymes involved in rhizobial GA biosynthesis share little or no homology with the plant and fungi proteins (Nett et al., 2017). Similarly, plants and microbes are able to produce auxin. The most common auxin indole-3-acetic acid (IAA) evolved independently in fungi (first detected in the spent media of a yeast culture), bacteria, and plants (Duca et al., 2014). In plants, auxin plays a role amongst others in cell division, tissue differentiation, and plant growth while in fungi, IAA affects cell expansion, disturbs cell division, and in some species induces spore germination (Fu et al., 2015). It is estimated that over 80% of the rhizospheric bacteria are capable of synthesizing IAA (Spaepen and Vanderleyden, 2011). For instance, both rhizobacterial strains, *Bacillus megaterium* UMCV1 and *Azospirillum brasilense* Sp245, produce auxins and induce root-architectural alterations such as increased number of lateral roots and longer root hairs (López-Bucio et al., 2007; Spaepen and Vanderleyden, 2011). In both plants and microbes, IAA is synthesized either by a tryptophan-dependent pathway or by a tryptophan-free way. The production of auxins in bacteria seems to depend on the availability of precursors in root secretions. L-tryptophan has been identified in root exudates and is suggested as the main precursor of the synthesis of bacterial auxins (Kamilova et al., 2006; Fu et al., 2015). Therefore, auxin concentration in the rhizosphere is highly dependent on plant–microbe interactions. The effect of auxin on bacteria is diverse; it may function as a signaling molecule affecting gene expression, regulate antibiotic synthesis, and pathogenesis antagonizing plant defense responses (Fu et al., 2015; Kunkel and Harper, 2018; Matilla et al., 2018). CKs are involved in the interactions between roots and soil microorganisms and have been reported to play an important role in defense against biotrophic pathogens. Arabidopsis plants treated with *trans*-zeatin before *P. syringae* pv. tomato DC3000 inoculation, led to decreased susceptibility to the bacterial pathogen (Choi et al., 2010). The convergent evolution of GA, IAA, and CK biosynthesis suggests that these molecules were favored as a widespread physiological code in plants and microbes.

The gaseous hormone ethylene is also produced by microbes, however, the main microbial modulation in the rhizosphere impacting ethylene balance in plants is the reduction of plant ethylene levels via degradation of its immediate precursor 1-aminocyclopropane-1-carboxylate (ACC) (Gamalero and Glick, 2015). The catabolic activity of the microbial enzyme ACC deaminase lowers local levels of the hormone in plants, and then the low ethylene concentration allows plant growth under stressed conditions. In return, ACC is a nitrogen source to the rhizosphere microbiota. This mutualistic relationship between plants and ACC

deaminase-producing bacteria has a great potential to promote plant stress tolerance as ethylene displays a wide range of biological effects in plants (Liu et al., 2019). As ethylene, ACC acts as a signaling molecule in several plant processes such as root–shoot signaling (Yoon and Kieber, 2013; Van de Poel, 2020), thus the interaction of plants with ACC deaminase-producing bacteria might decrease the degree of ACC signaling of specific plant functions. For instance, plant roots typically respond to flooding by synthesizing a high level of ACC. Due to lack of oxygen, ACC is translocated from roots to shoots, where it becomes a substrate for ACC oxidase and is converted to ethylene (Gamalero and Glick, 2015). Experiments with the "split-root" system demonstrated that a positive message (i.e. ACC) produced in roots was transmitted through the xylem and stimulated shoot ethylene production (Jackson, 2002). The abiotic stress plant hormone ABA is also produced by rhizosphere microbes and can be perceived by the plant hosts thereby improving drought resistance (e.g. *A. brasilense* sp 245; Cohen et al., 2008). ABA accumulation in soil can negatively affect seed germination, inhibit root growth and increase plant disease susceptibility (Yuzikhin et al., 2021). ABA root concentration balance interplays with other phytohormones in disease resistance, such as salicylic acid and ethylene. Interestingly, many rhizobacteria are capable of affecting the balance of one or more plant hormones. For example, *Burkholderia phytofirmans* PsJN affects both ethylene and auxin levels in plants. This same strain produces the autoinducer AHL that mediates QS in the rhizosphere and is crucial for root colonization (Zúñiga et al., 2013).

While AHL production by rhizosphere microbes is recognized to modulate plant gene expression and metabolism, host metabolites can cross-signal with microbial QS signals to modulate bacterial gene expression and root colonization (Joshi et al., 2021). The rhizosphere harbors a high amount of bacteria that employ QS mechanisms (Elasri et al., 2001). Among 129 bacterial isolates from cottonwood tree rhizosphere, 40% were tested positive for AHL production; all positive isolates belonged to the Proteobacteria phylum (Schaefer et al., 2013). A classical AHL QS system consists of a LuxI-type protein (AHL synthase) that interacts with the cognate LuxR-type protein (a transcription factor) (Steindler et al., 2008). Various *luxR* homologs were detected in the genomes of the cottonwood proteobacterial isolates, some of these homologs were suggested to be members of a subfamily of LuxRs that respond to plant signals rather than to bacterial AHLs (Schaefer et al., 2013). Bacterial AHLs can function as inter-kingdom signals on a widespread signaling network between plants and bacteria. As many plant beneficial and pathogenic bacteria require QS to successfully colonize the host plant, these bacteria can use their QS molecules to regulate plant growth (Schenk et al., 2012). Several plant species have been shown to respond to AHLs influencing and reprogramming plant gene expression (González and Venturi, 2013). Recently, four AHL molecules (*N*-(3-oxohexanoyl)-L-homoserine lactone [oxo-C6-HSL], *N*-(3-oxooctanoyl)-L-homoserine lactone [oxo-C8-HSL], *N*-(3-oxododecanoyl)-L-homoserine lactone [oxo-C12-HSL], and *N*-(3-oxotetradecanoyl)-L-homoserine lactone [oxo-C14-HSL]) and combinations of these molecules were tested for their effect on Arabidopsis growth and resistance against *P. syringae* pathovar tomato. Some of these AHL molecules, when treated independently, positively influenced plant growth, while others induced resistance by AHL-driven priming (Shrestha and Schikora, 2020). Many plant-associated bacteria (e.g. rhizobia, xanthomonads, and pseudomonads) have a LuxR-like protein that lacks an AHL synthase and these proteins are regarded as LuxR solo or orphan (Patankar and González, 2009; González and Venturi, 2013). LuxR solo proteins bind and respond to plant compounds. For instance, the plant phenylpropanoid *p*-coumaric acid accumulates in the rhizosphere. This metabolite activates the 4-coumaroyl-homoserine lactone synthase of *Bradyrhizobium* sp., which uses the plant-derived *p*-coumaric acid and endogenous *S*-adenosylmethionine to generate the hybrid signal molecule *p*-coumaroyl homoserine lactone (i.e. *p*-coumaroyl-HSL), which finally induces genes related to chemotaxis (Schaefer et al., 2008). Metabolism crosstalk is thus an emerging field in the rhizosphere inter-kingdom signaling, where plant host metabolites can be used as alternative substrates in bacteria (e.g. *p*-coumaroyl-HSL).

Future perspectives

The fusion of plant and microbial small molecules as a concerted effort (Wang and Seyedsayamdost, 2017), and the biosynthesis of metabolites induced by external signals or depending on the microbiome context (Korenblum and Aharoni, 2019) are unquestionably pertinent in complex ecosystems such as the rhizosphere. However, the effect of these phenomena is not restricted to the rhizosphere and likely influences the plant host at the "phytobiome scale" (i.e. the network of the whole plant with their microbiome, other organisms, and the environment; Leach et al., 2017). Systemic processes are particularly important in the microbiome–root–shoot–environment nexus; the rhizosphere microbiota can induce various physiological changes in plants, including promotion of growth, improved health, and modulation of root exudation (e.g. in SIREM). The understanding of the internal and external chemical signals induced by the rhizosphere microbiome in systemic responses will provide tools for better bioinoculants technology and exudate-oriented plant breeding. Moreover, in this "metabolic circular economy" in the rhizosphere, the chemical spectrum is extensive and there is likely no metabolic waste. It is estimated that one plant species produces a few thousand metabolites (Fernie et al., 2004), but only a few tens of root-derived metabolites are known to have a role on the rhizosphere microbiome (Table 1). Besides reducing this knowledge gap and systematic evaluation of the metabolic connectivity among root exudates and the rhizosphere microbiome in model and nonmodel plants further research on the spatial distribution of root-secreted metabolites along

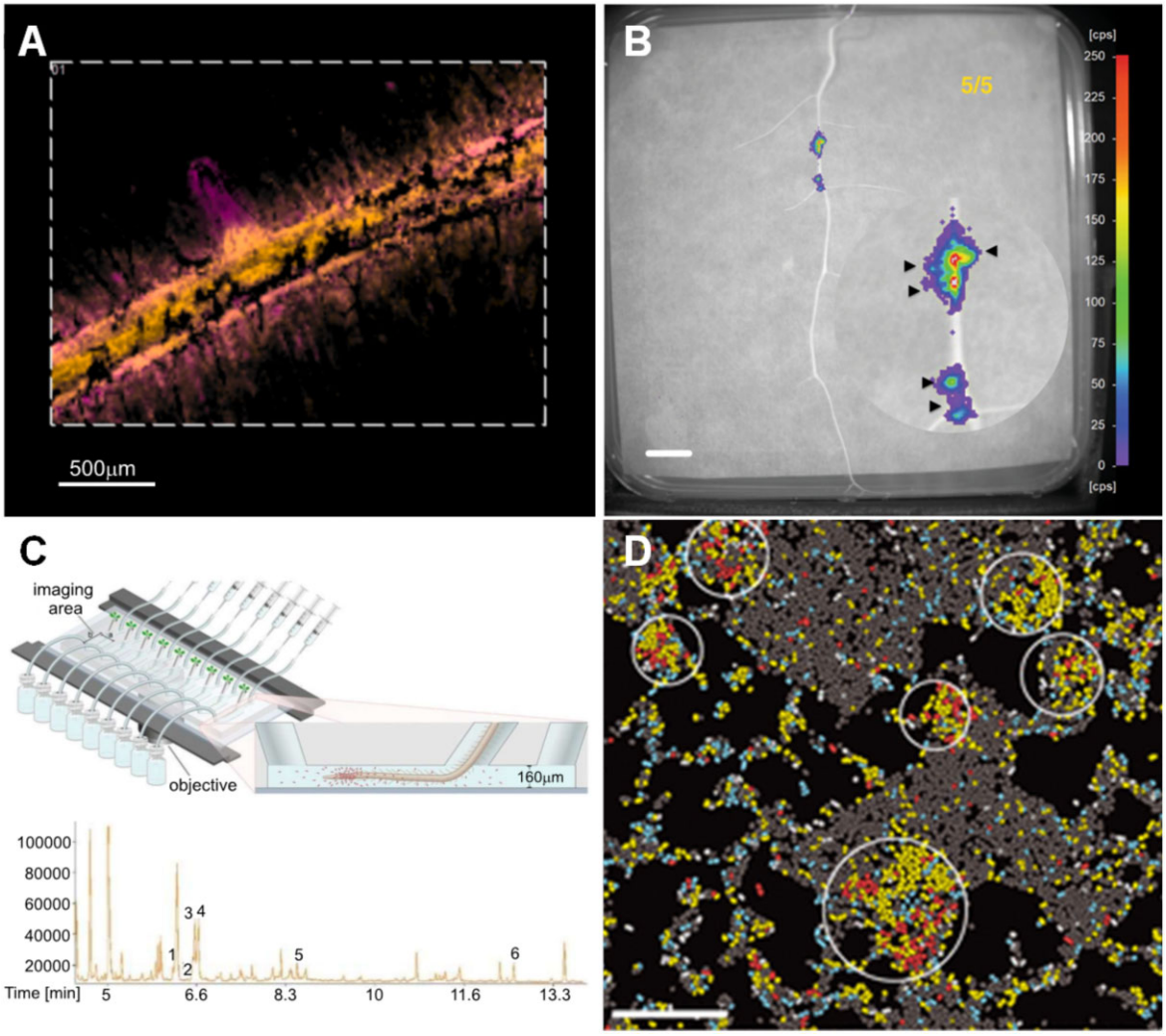

Figure 4 High-resolution methods to study chemical interactions in the rhizosphere. A, MSI-Imaging of tomato roots, metabolites are distributed in specific root regions as indicated by the overlap of false color images, hydroxytomatine (m/z 1050.54 ± 0.01 Da) in yellow and dehydrotomatine (m/z 1,032.54 ± 0.01 Da) in magenta (color hue was adjusted from Korenblum et al., 2020). B, NightOwl images of bioluminescence of *R. leguminosarum* Rlv3841/pOPS0046 (a rhizopine biosensor) growing on the surface of *M. sativa* roots allowed the detection of rhizopine exudation (Geddes et al., 2019). C, The microfluidic device TRIS consists of a series of 6.4 µL chambers, which allowed single-root exudate metabolomics. Ion chromatogram of a metabolic profile of single-root exudates analyzed by gas chromatography–mass spectrometry. Metabolites identified: 1, phosphoric acid; 2, isoleucine; 3, glycine; 4, succinic acid; 5, pyroglutamic acid; and 6, myoinositol (Massalha et al., 2017). D, Transcriptome imaging using par-seq FISH allowed the visualization of the spatial organization of transcriptional programs in *P. aeruginosa* at single-cell resolution. Using par-seq FISH, transcriptional states of individual cells can be identified and mapped onto the biofilm image (with permission from Dar et al., 2021).

the root axis using high-resolution methods will reveal detailed localization of metabolites in roots (Figure 4). These technologies include the combination of biosensors with microfluidic systems for in vivo spatiotemporal mapping of root secretion and microbial colonization (Massalha et al., 2017; Pini et al., 2017; Geddes et al., 2019) and MSI at the root cell-type resolution (Veličković et al., 2018; Korenblum et al., 2020). The spatial distribution of metabolites using these methods can be advanced by comparing mutants and wild-type plants. Additionally, spatially resolved metabolite localization at the single cell (Taylor et al., 2021) or the effect of metabolites on the microbiome transcriptomics at the single-cell resolution (Dar et al., 2021) are cutting-edge techniques that will further allow super-resolution of the metabolic coupling in the rhizosphere. Moreover, better understanding of the modulation of phytobiome metabolism will certainly advance the discovery of novel chemistries and the fundamental evolutionary trajectories of the metabolic crosstalk in the rhizosphere, that is, the chemically driven ecological rules in the rhizosphere. Gaining this knowledge is fundamental for the development of innovative strategies for sustainable agriculture and environmental protection.

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