
Gaining Insight into Plant Responses to Beneficial and Pathogenic Microorganisms Using Metabolomic and Transcriptomic Approaches

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Abstract

Plants are constantly interacting with microorganisms. Many of them have the potential to cause disease, while many other may establish beneficial interactions where plants enhance their ability to incorporate important nutrients and improve disease resistance. During these interactions, plants must regulate the expression of thousands of genes, which ultimately triggers distinct hormonal signaling pathways and affects the concentration of numerous metabolites. Transcriptomics and metabolomics have played a pivotal role in identifying the genes and metabolites involved in such responses, which has given crucial hints to refine our current strategies for plant protection and crop yield improvement. However, there is still a gap on our knowledge on many features that distinguish the interplay between plants and microorganisms. This chapter initially discusses the contributions of these high-throughput technologies to the understanding of this field of research and ends with future prospects in the search for interaction-specific biomarker genes and metabolites.

Keywords

Transcriptomics • Metabolomics • Plant-microobe interactions

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6.1 Introduction

The complexity inherent to plant-microorganism interactions is utterly stunning. These biological associations may present beneficial effects for the plant, such as those established with plant growth-promoting microorganisms (PMPMs), or rather act in detriment of plant fitness (e.g., pathogens) (Asai and Shirasu 2015). The study of this field has enormous implications in the development of the so-called green biotechnology, the combination of technological approaches tailored to improve crop production and quality.

As a consequence of the close contact with a multitude of microorganisms, plants have developed effective strategies to prevent the invasion by potential pathogens (Bernoux et al. 2011; Asai and Shirasu 2015). A first line of defense is exerted by a set of preformed chemical and physical barriers. For instance, the cuticle and cell wall thickness are crucial for plant defense, as well as the shape and size of the plant stomata, which may avoid the entrance of some microorganisms using these natural openings to invade plant tissues. In turn, many low molecular weight compounds collectively known as phytoanticipins and proteins classified as defensins are constantly synthesized to inhibit the growth and development of microorganisms (Tam et al. 2015; Pedras and Yaya 2015). In addition, plants have developed a bunch of surveillance systems to detect the presence of pathogens in the early stages of the infection and consequently trigger additional defensive responses. One of these systems requires the action of pattern recognition receptors (PRR), which are localized at the cell surface and detect foreign molecules associated with the pathogen, or pathogen-associated molecular patterns (PAMPs), and compounds derived from the degradation of self-structures, or damage-associated molecular patterns (DAMPs). As PAMPs and DAMPs are quite conserved among microbes, the defenses triggered following PAMP and DAMP detection (known as PTI for PAMP-triggered immunity) usually repel a broad spectrum of pathogens. In turn, many pathogens are able to overcome PTI by secreting effectors, some of which are injected directly into host plant cells and contribute to attenuate or completely block these initial plant defense responses. However, during evolution plants have developed various cytoplasmic proteins that detect the presence (or the activity) of effectors, an event that triggers the so-called effector-triggered immunity (ETI). This response simply reinforces previously activated defenses and also induces the activation of newly ones. Contrary to the multigenic nature of PTI, ETI requires the presence of one (or a few) particular gene in the plant and the microorganism, and it sometimes involves the activation of the hypersensitive response (HR), a type of programmed cell death in the host cells surrounding the infection site aimed to restrict the spreading of the disease. The evolution of microbial effectors and plant receptors is under constant selection pressure, which has originated disease cycles characterized by the appearance of novel pathogens overcoming ETI and the consequent resurgence of plant genotypes able to recognize and fight back against them (Dodds and Rathjen 2010). Several reviews have covered in detailed the functionality of plant immunity mechanisms and the forces driving plant defense evolution (Anderson et al. 2010; Dodds and Rathjen 2010; Bernoux et al. 2011; Asai and Shirasu 2015).

Both PTI and ETI involve the activation of an intricate network of signaling pathways where a large number of genes must be regulated in a very precise manner. Gene regulation leads to a tight control on the concentration and activity of metabolites and proteins. The advent of the so-called “omics” platforms has fostered a great progress in the identification of the most important components underlying successful plant defense responses. The term “omics” informally refers to different high-throughput techniques intended to characterize and quantify the entire pool of a kind of molecules in individual cells, tissues, or organisms under a given set of conditions. For instance, transcriptomic approaches provide information about overall gene expression levels simultaneously, while proteomics and metabolomics do it for proteins and metabolites, respectively. The analytical challenge associated to any of these approaches was one of the main setbacks that researchers faced not so long ago, as they usually required complicated, time-consuming, and expensive methods. Fortunately, this issue has been partially solved (and further advances should be expected) with the development of reliable and robust techniques that allow researchers to get an instantaneous snapshot of the entire collection of mRNAs, proteins, and metabolites in a relatively easy and inexpensive manner. Because they generate an enormous amount of data, perhaps the main challenge nowadays is our ability to analyze and interpret the results from these studies. In addition, as it is quite evident now that a single “omics” approach cannot decipher by itself the complexity pertaining cell physiology, the integration of multidimensional “omics” data has been proposed as an essential procedure (Zhang et al. 2010).

In this chapter, we first made a concise description of the most relevant techniques used in “omics” studies and later reviewed the general conclusions from transcriptomic and metabolomic works focused to unravel the molecular events occurring during the interactions between plants and microbes. Because of length restrictions, we will describe mostly those transcriptomic and metabolomic studies conducted to explore plant responses. However, readers should be aware that “omics” studies focused on microorganisms are also critical to have a fair comprehension of the interplay between both partners in the interaction.

6.1.1 Transcriptomic Platforms

The expression level of thousands of genes has been mostly assessed using two different methodologies, DNA microarrays (also known as DNA chips) and RNA-Seq technologies.

There are many protocols for DNA microarray-based studies. They basically require a first step of mRNA extraction from two or more samples under comparison, which must be then converted to cDNA by reverse transcriptase polymerase chain reaction (RT-PCR). Later, each sample is labeled using two distinct fluorochromes and mixed together previous to a hybridization step against individual DNA sequences spotted to a solid surface. Finally, the excess of non-hybridized cDNA is washed off and fluorescence determined by laser scanning. Relative

fluorescence of each fluorochrome indicates whether the gene is up- or downregulated in the experimental sample with respect to the control (Schena et al. 1995). Depending on the platform being used, the DNA probes spotted to the solid surface may be double-stranded or 16–20 bp oligonucleotides (Lodha and Basak 2012). Importantly, the construction of the DNA chip requires the pre-existing knowledge of the genomic sequence of the organism under study.

Even though microarrays are at the top among the most used platforms for transcriptomic studies, the considerable improvements achieved in sequencing technologies in the last years have led to the development of novel sequence-based approaches. These methods have emerged as the dominant platforms and have revolutionized the transcriptional landscape. The most widely used of these new methodologies is RNA-Seq. In this method, isolated RNA is used to construct a double-stranded cDNA library, and each cDNA is later individually sequenced (Wang et al. 2009). There are several methods for massive sequencing, all requiring a first step of *in vitro* cloning and amplification of the individual cDNA strands (Qian et al. 2014). Reads can be counted, which allows to infer the level of expression of a defined gene. The main obstacle with RNA-Seq is the fact that sequencing produces millions of short sequences ranging from 25 to 450 bp, which constitute a serious bioinformatic challenge. Nevertheless, the advent of powerful software in the last years has accelerated the mapping and assembling of these sequences, thus speeding up data management and interpretation.

6.1.2 Metabolomics

Metabolomics is the combination of techniques that monitor the metabolome, that is, the pool of small organic molecules defining a biological sample. In a standard metabolomic procedure, metabolites are solvent extracted from biological samples and then detected and quantified using different chemical detection procedures. In this trend, mass spectrometry (MS) is a powerful tool for studying metabolites due to its sensitivity and flexibility for detection of different classes of molecules. Besides, in order to enhance the capability to unravel the complexity of biological extracts, MS has been coupled to chromatography, a combination known as a “metabolomic platform.” The most widely used platforms are liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS). Although there are other platforms, like Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS) or nuclear magnetic resonance spectroscopy (NMR), they have some disadvantages that make them inappropriate to profile complex mixture of compounds (Kopka et al. 2004).

The great amount of data generated with MS-associated techniques makes the annotation of the detected molecular features the bottleneck in metabolomic studies (Wishart 2011). This has given rise to the development of two workflows: targeted and nontargeted metabolomics. Readers should be aware that nontargeted metabolomics is also referred as “untargeted,” “unbiased,” or “global” metabolomics (Heuberger et al. 2014). Targeted metabolomics is focused on the analysis of a particular set of metabolites, thus requiring the knowledge of the compounds of interest

in advance. There are different ways to target the metabolomic profile to a certain group of molecules, such as the optimization of the extraction protocol and the use of solvents with different polarities and pH to maximize recovery of the desired compounds. This reduction in the complexity of the sample allows a better calibration of the spectrometer and significantly raises the sensitivity in the detection of a particular group of metabolites. In addition, it gathers data of metabolites with known masses and retention times and uses data analysis procedures that are relatively simple. Data normalization is conducted employing isotope-labeled internal standards for each compound of interest or a class of compounds. The main disadvantages of targeted workflows are the demand for authentic standards as well as the time, labor, and costs inherent to the optimization of these methods. On the other hand, nontargeted workflows are designed to globally profile all detectable metabolites in the sample. This is perhaps the main advantage of this approach, as it is able to detect not only the same metabolites than in a targeted design but it can also collect novel chemical identities. Therefore, in this case, the extraction and detection procedures must be optimized to include all different classes of metabolites. One of the main issues in nontargeted analyses is the identification and annotation of unknown compounds. This is relatively difficult as every molecule ionized in MS prior detection leads to several mass signals. One way to solve this problem is to cluster and cure this redundant data by computational procedures. Once the spectrometric data are cured, molecular features are annotated as metabolites by comparing data against different spectral databases. In those cases where a perfect match is not found, partial matches may involve molecules with similar structures.

In summary, targeted workflows require significant efforts to optimize the experiment, and they result in only the identification of a defined group of compounds. However, they produce less-complex data and allow more confident statistical analyses. On the other hand, nontargeted metabolomic workflows might lead to the discovery of novel compounds by using relatively simple analytical procedures; even so they require higher efforts in the analysis and interpretation of the resulting data.

6.2 High-Throughput Analysis of Plant-Microbe Interactions

The technologies described above have made an enormous contribution to biological research and accelerated in an impressive way our knowledge of the molecular events that govern plant-microbe interactions. They are becoming gradually less expensive, require less effort, and may be performed in almost any organism. Perhaps the main concern in future studies will be the interpretation of the extensive amount of data generated as well as the integration of results coming from different “omics” technologies. It is important to understand that plant responses may vary from a situation where a few cells are engaged in the interaction (as occurs generally with pathogens unable to overcome the first passive lines of defense) to a very different situation where cells are seriously affected (as in the case of compatible pathogens) (see Fig. 6.1). In addition, the responses change considerably over time, and samples may include a mosaic of cells

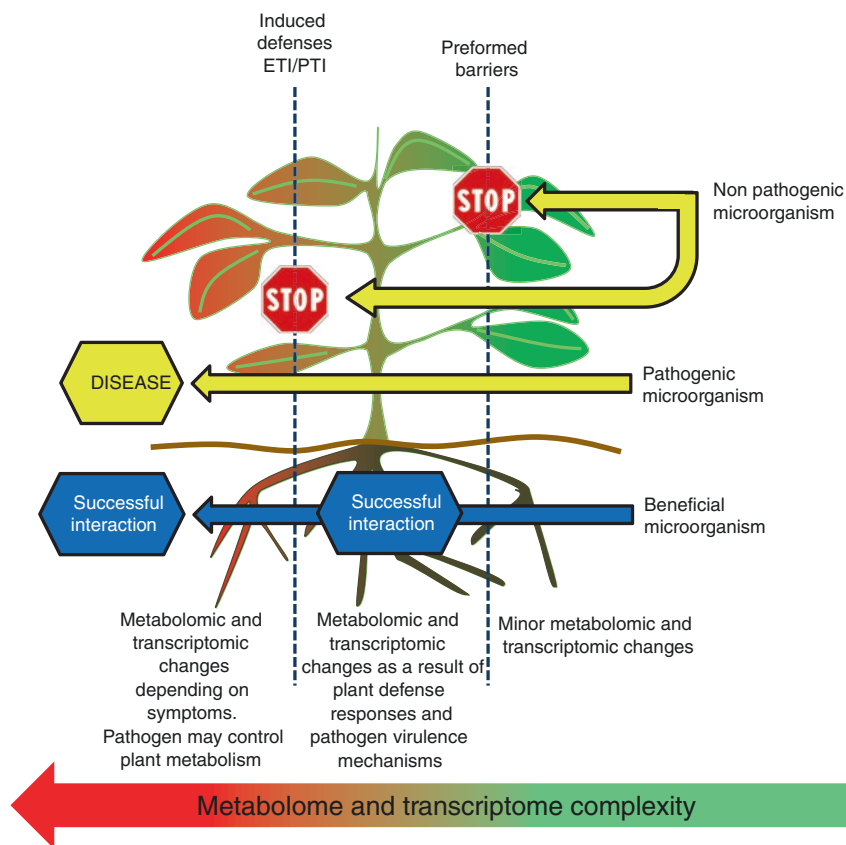


Fig. 6.1 Scheme depicting molecular modifications that could occur during the interactions between plants and microorganisms. Nonpathogenic microorganisms fail to overcome the first line of plant preformed barriers or induce responses associated to PTI and ETI. In turn, pathogens are able to attenuate or block these defensive mechanisms and establish the disease. Even though beneficial microorganisms evade preformed barriers, they may not necessarily induce full additional responses as those triggered by other invading microorganisms. Transcriptomic and metabolomic complexity is expected to grow proportionally to the perturbation on plant cell physiology

with different physiological status and belong to different organisms. Therefore, when interpreting omics data, researchers should consider the temporal evolution of plant-microbe interactions and take special care on the type of samples under analysis.

6.2.1 Transcriptomic Analysis of Plant Responses During Their Interactions with Microbes

6.2.1.1 Pathogenic Microorganisms

Currently, we have a very good idea of the main hallmarks of the transcriptomic landscape in plant responses to pathogens. However, it is rather problematic to identify common patterns of responses among all the plant species studied. This is so

because the specific responses depend not only on the plant species but also on other factors as the interacting microorganisms, the type of interaction, and the plant organs involved. This limits our capability to extrapolate the results obtained from a particular plant-microbe interaction to another. Nevertheless, in spite of these setbacks, we are still able to look at the entire picture and make some broad conclusions that may be considered when working with related plant species. In this trend, a bunch of plant responses regulated at the transcription level might be expected to occur during any type of interaction, such as the production of antimicrobial compounds and the activation of upstream gene regulatory factors and common signaling cascades. There are, of course, appreciable quantitative as well as qualitative differences among all these responses, which ultimately decide the fate of the interaction.

Global transcriptomic analysis made a substantial contribution to tear down a long-standing paradigm on plant-pathogen interactions, the assumption that the defense responses mediated by salicylic acid (SA) protect the plant against biotrophic microorganisms (those colonizing and obtaining nutrients from living tissues), whereas those responses induced by hormones like jasmonic acid (JA) and ethylene (Et) operate against necrotrophic microorganisms (which kill plant cells and feed on them) (Glazebrook 2005). It was also proposed that both sets of activation mechanisms act in an antagonistic mode. However, gene expression profiling demonstrated that hormonal cross talk is not such a simple mechanism and exposed a very different scenario, in which significant overlapping occurs between both signaling networks (De Vos et al. 2005; Salzman et al. 2005; Garg et al. 2012; Okamoto et al. 2012). The work by Garg et al. (2012) gives a good example of this statement. These authors evaluated global gene transcription after treating rice seedlings with SA, JA, Et, or other phytohormones such as auxins, cytokinins, and abscisic acid (ABA). The range of genes being altered by these hormones ranged from a maximum of 3635 (ABA treatment) to a minimum of 183 (in seedlings treated with the ethylene precursor 1-aminocyclopropane-1-carboxylic acid, ACC), indicating that at least in their experimental conditions, the effects of plant hormones on gene regulation were significantly different. Nevertheless, 28% of these regulated genes were responsive to two or more treatments; most of them showed a similar response (upregulated or downregulated in all treatments), while a few showed contrasting responses (upregulated in a treatment and downregulated in others). The extension of the overlapping response was quite high in some cases, demonstrating that hormones may play crucial roles in the same response. For instance, 91% and 81% of the genes regulated by auxin were also responsive to SA and ABA, respectively. Importantly, the authors also showed a significant overlapping between the SA and JA responses. It should be noted that the similarities between these pathways might be even higher since hormones can regulate the same cellular processes by nonoverlapping transcriptional responses. Similar conclusions were drawn from global transcriptional studies in other model systems (Salzman et al. 2005; Nemhauser et al. 2006; Goda et al. 2008; Okamoto et al. 2012; Wang et al. 2013). Based on this, it is clear now that hormones work in a cooperative manner in the activation of a subset of defense mechanisms but may antagonize the activation of other responses. Plants must then interpret the combination of hormone-induced pathways to respond

properly to pathogen attack. Moreover, transcriptomics is helping to uncover the link between novel molecules and some of defense mechanisms activated by plant hormones. For instance, microarray analysis of *Arabidopsis* lines with different levels of the polyamine spermine demonstrated that this compound regulates at the transcription level a broad spectrum of genes associated to biotic and abiotic stress (Gonzalez et al. 2011). Likewise, it was shown that potato plants treated with β -aminobutyric acid (BABA) are resistant against *Phytophthora infestans*, which might be related to its positive effect on the expression of PR proteins and phytoalexin biosynthesis (Bengtsson et al. 2014).

Global gene expression analysis also showed that plants shift their primary metabolism to a higher demand for energy and biosynthetic rate during defense (Scheideler et al. 2002). This seemed to contradict the observation that photosynthesis and chlorophyll biosynthesis are downregulated upon contact with pathogens (Bilgin et al. 2010), which was thought to preserve hard-earned metabolites to build up defense responses. However, more recent studies showed that plants facing the attack of a microorganism upregulate main primary metabolic pathways, such as those involved in the synthesis and degradation of carbohydrates, amino acids, and lipids (Rojas et al. 2014). By these means, plants are able to generate important energetic molecules and, by the same token, other signaling and active compounds that drive the defense responses. In particular, the induction of genes involved in glycolysis, the pentose phosphate and the tricarboxylic acid pathways, electron transport, and ATP biosynthesis are thought to provide energy and favor downstream defense processes as radical oxygen species (ROS) generation and expression of PR proteins. Collectively, these works suggest that energy is acquired from an increase in the respiratory metabolism and a higher import of hexoses by cells engaged in the defense against the pathogen (Essmann et al. 2008; Proels and Huckelhoven 2014; Rojas et al. 2014). Even though transcriptomics is giving a good hint of the function of the plant metabolism in plant-pathogen interactions, a deeper exploration remains to be done in order to assess the main impact of a single metabolite in this process. The shift on the primary metabolism occurs mainly during incompatible interactions, where the disease is successfully suppressed. By the contrary, the patterns of global gene expression might be considerably different in compatible interactions, where it results from the activation of plant responses to pathogen perception as well as the action of virulence mechanisms triggered by the pathogen (as virulence factors are secreted by biotrophs to modulate plant metabolism in its own favor or by necrotrophs to affect plant cell fitness).

For many microorganisms, to exert a tight control of the plant metabolism may be crucial to support the infection process (Okmen and Doehlemann 2014). For instance, it has been demonstrated by microarray experiments that the expression of plant heat-shock proteins (HSPs) is induced during viral infections (Whitham et al. 2003; Senthil et al. 2005) and that HSPs are important to ensure proper synthesis of viral proteins (Qanungo et al. 2004). In the same line of evidence, viral particles of BNYPV (*Beet necrotic yellow vein virus*) containing the single-stranded RNA known as RNA4 modify the expression of several genes from *Nicotiana*

benthamiana involved in RNA silencing, ubiquitin-proteasome pathway, cellulose synthesis, and gibberellin metabolism, which may contribute to virus multiplication in the infected leaves (Fan et al. 2014). Similarly, *Plasmodiophora brassicae* causes the upregulation of brassinosteroid synthesis and signal perception genes in *Arabidopsis*, and it has been demonstrated that this process is essential for symptom development (Schuller et al. 2014). Biotrophic pathogens also provoke the attenuation of plant defense responses. Thus, microarrays have demonstrated that the establishment of successful biotrophy by the maize fungal pathogen *Ustilago maydis* leads to a suppression of several defense responses triggered during the initial phase of the interaction, such as PR protein expression and phytoalexin synthesis (Doehlemann et al. 2008). The ability of the pathogen to attenuate the initial plant responses and avoid subsequent massive changes in gene expression is a key element for complete virulence (Truman et al. 2006; van de Mortel et al. 2007).

Transcriptomics has been an attractive approach to compare plant responses to compatible and incompatible pathogens. The initial thought was that the main cellular functions responsible for pathogen recognition and control could be distinguished by cutting off all those genes being exclusively regulated during the incompatible interactions. However, it was clear from the beginning that both compatible and incompatible pathogens roughly induce the same patterns of cellular functions and that the outcome of the interactions depends rather on complex quantitative and temporal differences of common transcribed genes or a different set of genes contributing to the same functional category (Tao et al. 2003; Zimmerli et al. 2004; Zou et al. 2005; Rinaldi et al. 2007; Baebler et al. 2009; Zellerhoff et al. 2010; Wichmann et al. 2011; Bagnaresi et al. 2012; Bai et al. 2013; Bordenave et al. 2013; Chen et al. 2013). For instance, Bai et al. (2013) demonstrated that the transcriptional responses in roots of banana cultivars with different susceptibilities to *Fusarium oxysporum* were quite alike. However, the resistant cultivar reprogrammed a greater set of genes in a faster manner against the fungus. Most of these genes were related to biotic stress, such as PR proteins, cell wall metabolism, and PAMP receptors. In turn, the susceptible cultivar over-expressed genes associated to HR and senescence, suggesting that these processes favor fungal colonization. In turn, very similar functional categories were demonstrated to be induced in susceptible and resistant ecotypes of *Solanum lycopersicum* and *Solanum tuberosum* against the *Tomato yellow leaf curl virus* (TYLCV) and the *Potato virus Y* (NTN), respectively, but they differed in the expression levels of a group of defense genes. Thus, susceptible cultivars showed a general gene shutting-off when challenged by the virus, whereas resistant cultivars were able to induce PR genes, WRKY transcriptional factors, protein kinases, and enzymes involved in the secondary metabolism (Baebler et al. 2009; Chen et al. 2013). Interestingly, transcriptomic studies also suggest that resistance may be associated to higher basal expression of important genes rather than their upregulation after pathogen perception. In this trend, several defense genes were found to be highly expressed in non-inoculated leaves of the ecotype Gifu B-129 of *Lotus japonicus* when compared to the ecotype MG-20, showing moderately resistant and susceptible phenotypes against *Pseudomonas*

syringae pv. tomato DC3000, respectively. Importantly, several of these genes were upregulated in MG-20 after bacterial infiltration (Bordenave et al. 2013). Comparable results seem to explain at least in part the resistance of the rice variety CL 161 to *Burkholderia glumae* (Magbanua et al. 2014).

6.2.1.2 Beneficial Microbes

Plants may be benefited from interactions established with microorganisms including different kinds of fungi, bacteria, and yeasts. Because of their effect on the plant hosts, these microorganisms are commonly known as plant growth-promoting microorganisms (PGPM). Mechanisms of growth promotion by well-studied PGPMs include phosphate solubilization, production of phytohormones, nitrogen fixation (performed by diazotrophic microorganisms), and production of siderophores to facilitate the transport of ferric iron into plant cells (Glick 1995; Bloemberg and Lugtenberg 2001). PGPMs can also stimulate plant growth by preventing the deleterious effects of phytopathogenic microorganisms. In this case, they act as biological control agents by direct antagonistic effects on pathogenic organisms or indirectly by priming plant defense responses, a state that allows the plant to react more rapidly to attacking pathogens (Bloemberg and Lugtenberg 2001; Haas and Keel 2003; Ryu et al. 2004; Balmer et al. 2015). In the light of public concern about the use of agrochemicals and the need to find alternative methods for increasing plant yield and protection against pathogenic microorganisms, the abovementioned features of PGPMs give them an unlimited potential for agronomic use. The best-known PGPMs are microorganisms able to colonize the rhizosphere and, in some cases, invade root interior and establish endophytic populations (Kloepper et al. 1999). In addition, some PGPMs are capable to pass the root endodermis barrier and reach the vascular system, from where they subsequently colonize other organs of the plant (Kobayashi and Palumbo 2000; Lundberg et al. 2012; Romero et al. 2014). Even though they usually enter plants through roots, endophytic communities can also be originated from the phyllosphere (aboveground portions of plants), the anthosphere (flowers), and the spermosphere (seeds) (Hallmann et al. 1997).

Among the different PGPMs, bacteria are probably the most studied microorganisms of this group. In the last years, many works have been published describing the isolation and characterization of several plant growth-promoting bacteria (PGPB) from different environments and hosts (Luna et al. 2012; Abraham et al. 2013; Rashid et al. 2012; Huang et al. 2013; Romero et al. 2015). However, the molecular mechanisms underlying the beneficial effects provoked by most of these microorganisms are not always easy to be established. Many attempts have been made to address this issue by using transcriptomic approaches in model plants and microorganisms. van de Mortel et al. (2012) analyzed the transcriptomic changes induced by the rhizobacterium *Pseudomonas fluorescens* SS101 (Pf.SS101) in *Arabidopsis*. Seed treatment with Pf.SS101 resulted in a total of 1179 and 920 differentially expressed genes in roots and leaves, respectively. Functional classification of the 556 genes upregulated in roots showed a large group belonging to functional categories related to defense, such as general stress response, root morphogenesis, metal ion transport, secondary metabolism (mainly those from the glucosinolate

biosynthesis), and SA signaling. A similar trend was observed in leaves, where a large proportion of the responsive transcripts were involved in SA signaling and secondary metabolism (phenylpropanoids, flavonoids, glucosinolates, and camalexin biosynthesis pathways). In turn, downregulated genes in these tissues were associated to hormone signaling and abiotic factors such as temperature, desiccation, and oxidative stress. Importantly, many of the upregulated genes related to defense in roots and leaves of inoculated plants were previously described to participate in PTI activation (Thilmony et al. 2006). In a similar study, Wang et al. (2005) analyzed the transcriptional changes induced by *P. fluorescens* strain FPT9601-T5 in *Arabidopsis* shoots. The authors found that 95 genes were upregulated during the infection, whereas 105 were downregulated. The majority of these genes belong to functional categories associated to metabolism, transcription, cellular communication/signal transduction mechanism, cell rescue, development, and disease resistance (PR proteins, WRKY transcription factors, secondary metabolism, and stress response proteins such as glutathione S-transferase and peroxidase). Moreover, among the upregulated genes, these authors found many transcripts that could be responsible for plant-growth promotion, such as auxin-induced genes as well as genes involved in the metabolism of C compounds and carbohydrates. Auxin-induced genes were also induced in *Arabidopsis* plants inoculated with *P. chlororaphis*, along with many transcripts related to disease resistance such as the PR proteins, the broad-spectrum mildew resistance gene RPW, and the defense-associated transcription factor WRKY18 (Cho et al. 2013). Similarly, genes involved in stress response, oxidative burst, response to auxin, and wounding were induced in this plant species following the inoculation with *P. thivervalensis* MLG45, whereas many transcripts related to photosynthesis and chloroplast function were downregulated (Cartieaux et al. 2003). An additional study focused on the transcriptional changes induced in the aerial tissues of *Arabidopsis* by root-colonizing bacteria was done by Verhagen et al. (2004) using *P. fluorescens* strain WCS417r, which is known to induce systemic resistance against different pathogens. Interestingly, these authors found that bacterial inoculation provoked the upregulation of a set of genes in leaves involved in the JA and Et signaling. These observations are in agreement with previous findings demonstrating the requirement of these plant hormones for full expression of induced systemic resistance (ISR) (Pieterse et al. 1998, 2000).

This trend of defense activation/auxin pathway induction is not only restricted to infections by *Pseudomonas* strains, since it was also described to occur following inoculation with *Bacillus subtilis* (Lakshmanan et al. 2013). Interestingly, this work also showed that “transcription” is among the most represented functional categories in the downregulated group. This category is comprised of members from two major transcription factor families, ERF (ethylene response factor)/AP2 and MYB, which have been widely associated to defense, indicating that some of the signaling pathways related to plant defense are suppressed during the interaction of plants with endophytic bacteria. The work by Wang et al. (2005) also identifies four nodulin-like genes among those activated after bacterial inoculation. As nodulin proteins play crucial roles during symbiotic nitrogen fixation with rhizobia, it was proposed that these PGPBs and rhizobia might share common signaling pathways.

The upregulation of genes involved in auxin biosynthesis was also observed during the interaction between canola and *Pseudomonas putida* UW4 (Stearns et al. 2012) and *Arabidopsis/Burkholderia phytofirmans* PsJN (Poupin et al. 2013). In the last system, the authors also reported the upregulation of different genes involved in the biosynthesis and signaling effects of other phytohormones such as gibberellins, SA, JA, and Et. Auxin-responsive genes, such as a putative auxin-regulated protein, a xyloglucan endo-1,4- β -D-glucanase precursor, and the heat-/auxin-/ethylene-/wounding-induced small protein, were also induced in *Arabidopsis* by the PGPMs *P. thivervalensis* MLG45 and *P. fluorescens* FPT9601-T5 (Cartieaux et al. 2003; Wang et al. 2005). Noteworthy, *P. fluorescens* WCS417r, *P. fluorescens* FPT9601-T5, and *Pseudomonas chlororaphis* O6 colonization led to downregulation of *Arabidopsis* genes involved in the Et signaling pathway (Verhagen et al. 2004; Wang et al. 2005; Cho et al. 2013). Interestingly, it was shown that during the interaction between *Arabidopsis* and *Azospirillum brasilense* Sp245, genes from the GH3 family (GH3.2, GH3.3, GH3.4, GH3.5, and GH3.12) were upregulated. Members of the GH3 family encode for enzymes that conjugate indole acetic acid to amino acids, an important function in auxin homeostasis (Spaepen et al. 2014). In this work, plants were also inoculated with a mutant strain of *A. brasilense* unable to produce IAA, which provoked just a milder induction of GH3.3 and GH3.4. These results suggest that the induction in the auxin-response genes during beneficial interactions could be, at least in part, due to the production of IAA by microorganisms.

The symbiotic interactions between nitrogen-fixing rhizobia and legume plants require the coordinated expression of numerous genes. The activation of the plant transcriptional machinery after plant-rhizobia mutual recognition leads to the formation of root nodules, specialized structures for nitrogen fixation and assimilation (Popp and Ott 2011). Microarray and RNA-Seq approaches have been used to profile gene expression during nodule development. Moreau et al. (2011) and Maunoury et al. (2010) used a series of *Sinorhizobium meliloti* mutants, as well as mutant lines of the model legume *Medicago truncatula* with impaired symbiotic properties, in order to analyze transcriptional reprogramming during different nodule developmental stages. A similar approach was used by Hogslund et al. (2009) to study the interaction between *Mesorhizobium loti* and *Lotus japonicus*. By these means, these works were able to distinguish different groups of genes depending on their expression patterns. The first phase of nodule development was usually characterized by the repression of many defense-associated genes, particularly those belonging to the phenylpropanoid pathway, suggesting that plant defense is switched off from the beginning. The rest of the process is accompanied by a transient induction of genes regulating cell cycle progression and protein synthesis followed by the activation of genes from the secretory pathway. It is thought that the last groups of genes are in charge of nodule organogenesis and maintenance, respectively. This process was also explored in depth by Roux et al. (2014), using RNA-Seq coupled to laser microdissection of nodule regions. An important finding of these authors was that some of the key genes controlling the root apical meristem seem to participate also

in the nodule meristem region, suggesting that both processes share common regulatory pathways.

Plants also establish interactions with nonpathogenic beneficial fungi. For instance, *Piriformospora indica* has a broad spectrum of mutualistic symbiosis with plants. Schäfer et al. (2009) analyzed the transcriptomic changes induced by the colonization of *P. indica* in barley roots at different stages of the infection, from the development of the fungus on the root surface to penetration and root cell colonization. They observed that the number of genes differentially expressed increased with the progress of the colonization process. The most represented functional categories were defense/stress response, signaling, secondary metabolism, transport, transcription, and protein biosynthesis. Most of the upregulated transcripts coded for many proteins are involved in regulation of cell death, and genes are involved in the biosynthesis of phytoalexins, carotenoids, and gibberellins. In addition, as observed with plant-beneficial bacteria interactions, colonization by *P. indica* induces the expression of genes involved in auxin biosynthesis and signaling. Lahrman et al. (2015) compared the response to *P. indica* with that induced by the related fungus *Sebacina vermifera*. This work showed that both responses were quite similar, particularly in the timing of induction of genes responsible for the biosynthesis of secondary metabolites such as glucosinolates, phytoalexins, and triterpenoids. At the same time, key regulators in the signaling pathways of SA, JA, and Et were also upregulated in both systems. Interestingly, these modifications in gene expression were accompanied by an increase in the concentration of JA in inoculated plants and a decrease of SA along with the accumulation of its catabolic products 2,3- and 2,5-dihydroxybenzoic acid (2,3-DHBA and 2,5-DHBA, respectively). As two genes for the conversion of SA to 2,3-DHBA and 2,5-DHBA were among those induced by the fungi, it was suggested that these symbionts do not repress the production of SA but induce the SA catabolism by which plants regulate the concentrations of the phytohormone (Lahrman et al. 2015). Similarly, the endophytic colonization of barley by *P. indica* or the nematophagous fungus *Pochonia chlamydosporia* also provokes the upregulation of genes involved in the metabolism of auxins, Et, and JA (Larriba et al. 2015).

Fungi from the genera *Trichoderma* are broadly used as biocontrol agents. Mathys et al. (2012) analyzed the transcriptional regulation during the induction of ISR in *Arabidopsis* by *T. hamatum* and compared it to the defense responses elicited by the necrotrophic pathogen *Botrytis cinerea*. Both responses were found to overlap in the induction of HR-related genes, as well as different components of the response to chitin, and intermediate compounds of the SA and ABA pathways. On the other hand, the main differences were found in the induction of negative regulators of the defense mechanisms, which were upregulated only by *T. hamatum*. These results differ considerably to those obtained using *T. harzianum*, another species of this genus. In this case, the colonization of *Arabidopsis* plants downregulated the SA signaling pathway, while typical markers for the JA defense cascade remained unaffected (Morán-Díez et al. 2012). The basis explaining such differences has not yet been established.

Arbuscular mycorrhizal fungi (AMF) are obligate biotrophs that colonize inter- and intracellularly the root cortex of host plants forming specialized structures called arbuscules and assist plants in obtaining important nutrients from the soil (Parniske 2008). This interaction also provokes profound changes in the transcriptomic profile of plants. Thus, tomato roots inoculated with two different species of AMF, *Glomus mosseae* and *Glomus intraradices*, showed the upregulation of defense genes encoding a chitinase, glutathione S-transferase, β -1,3-glucanase, patatin, β -D-xylosidase, pathogenesis PR10-like protein, and DXS-2, a key enzyme of the mevalonate-independent pathway of carotenoid biosynthesis (López-Ráez et al. 2010). Interestingly, JA- and oxylipin-related genes were induced in mycorrhizal plants, but no other changes were observed in genes related to ABA, SA, or Et signaling. A large group of genes induced in *L. japonicus* during the colonization by the AMF *Gigaspora margarita* were related to membrane synthesis and cell wall architecture (Guether et al. 2009). This observation provides a strong support for the hypothesis that the plant host plays an active role in the restructuring of roots to facilitate the infection process. A recent microarray analysis showed that exudates from *G. margarita* spores are able to induce a strong response in roots of *L. japonicus*. This response includes an increased expression of many defense genes at the onset of the treatment, which are later on downregulated to let the infection proceed normally (Giovannetti et al. 2015).

6.3 Changes of the Plant Metabolome During Plant-Microbe Interactions

Metabolomics lets us detect and quantify the set of metabolites that define any time point in the interaction between plant and microbes. As metabolites represent the final step of all the regulatory networks triggered during these interactions, the analysis of metabolomic profiles brings our conclusions closer to phenotype (Feussner and Polle 2015). One of the main benefits of this approach resides in the fact that in contrast to transcriptomics and proteomics, it does not require previous knowledge on the genome and transcriptome of the studied organisms. This means that metabolomic approaches can be easily focused in any plant, regardless of the availability of genomic information.

6.3.1 Pathogenic Interactions

Even though in a lesser extent than transcriptomics, metabolic profiling has been used to investigate the global responses of plants against pathogenic microorganisms. In this trend, Ward et al. (2010) evaluated the changes in the metabolic profiles of *Arabidopsis* plants infected with virulent and avirulent strains of *P. syringae*. These authors found that the responses to these strains differ in the changes associated to the abundance of some specific metabolites. These changes involved molecules such as amino acids and nitrogenous compounds, as well as carbohydrates and

ROS modulators. Interestingly, many of these differences were observed in metabolites with very low abundance, suggesting that the outcome of the interaction relies on subtle but very important changes in the defense metabolome. Perhaps the most significant reconfiguration was observed in the levels of aromatic amino acids. In agreement with this, it has been shown that the metabolism of tryptophan is dramatically activated in *Arabidopsis* after treatment with a bacterial lipopolysaccharide (which functions as a MAMP and elicits plant defense responses), a mechanism supposed to fuel the synthesis of the antimicrobial phytoalexin camalexin (Beets et al. 2012). Additional works should be addressed to understand the real impact of these metabolites in the outcome of the interactions. Phytoalexins belonging to the sesquiterpene alkaloid family were also shown to accumulate in potato sprouts infected by the fungus *Rhizoctonia solani* (Aliferis and Jabaji 2012), a phenomenon that could help to delay pathogen multiplication. This work also demonstrated that potato plants respond to the pathogen with the production of a vast amount of other defense molecules with antimicrobial activity, such as oxidized fatty acids and organic acids, including oxalic acid and ferulic acid.

Some studies focused on the effect of pathogen effectors and other known defense elicitors. For instance, rice plants exposed to chitin accumulate diterpenoid phytoalexins, which was demonstrated to be activated by a signaling pathway regulated by the MAPK kinase OsMKK4 (Kishi-Kaboshi et al. 2010). In turn, the effect of the priming agent BABA in *Arabidopsis* plants was also analyzed, which was shown to induce the accumulation of indole-3-carboxylic acid, whereas other indolic compounds remained unaltered (Gamir et al. 2012). It was proposed that the production of this intermediate compound accelerates callose deposition and downregulates the production of phytoalexins. Similar studies were conducted in tobacco cells exposed to the plant stress-derived metabolite isonitrosoacetophenone and the fungal steroid ergosterol (Madala et al. 2013; Tugizimana et al. 2014), which provoked different variations in the concentration of important components of the secondary metabolism (terpenoids, coumarins, lignin, phenylpropanoids, and flavonoids) and hormones. All of these investigations represent an invaluable contribution to the understanding of the molecular components that orchestrate plant defense responses. Metabolomic profiling was essential to understand the functionality of a chorismate mutase enzyme secreted by *U. maydis* during the biotrophic phase of infection of maize plants. Interestingly, this protein is incorporated by plant cells, spreads to adjacent cells, and perturbs their metabolism, contributing to attenuate plant defense by diverting the synthesis of SA to the production of phenylpropanoids such as coumaroyl and caffeoylquinic acid, syringin, and lignan (Djamei et al. 2011). Likewise, a metabolomic analysis has recently shown that the effector protein Tin2 from *U. maydis* also promotes plant colonization by activating anthocyanin synthesis at the expenses of other important plant defense compounds (Tanaka et al. 2014). These results demonstrated that a fine-tuned regulation of the host metabolome must be coordinated by the pathogen for a successful infection. This is also evident in the interaction between wheat and the hemibiotrophic pathogen *Zymoseptoria tritici* (Rudd et al. 2015). This fungus grows initially in the extracellular space of plant tissues and shows a long symptomless biotrophic phase but then develops a fast

necrotrophic phase and then kills host cells. Metabolic profiling conducted in colonized plants has shown that during the initial phase of the infection, the host physiology remains unaltered, and there is no activation of plant defense responses. A comparison of these results with those from studies performed on in vitro cultures of the fungus suggests that the microorganism supports its growth during this stage at the expense of the oxidation of stored lipids and fatty acids. This sub-utilization of plant-derived nutrients coincides with the induction in the expression of fungal genes that presumably suppress plant defense responses. However, this phase is followed by a notable switch in plant and fungal physiology, during which the fungus down-regulates the expression of effectors and activates cell wall-degrading enzymes. Accordingly, plant defense signaling is induced leading to host cell death.

With the aim to explore the molecular basis explaining plant resistance, metabolomics has been used to compare the time-course changes in metabolite concentration between resistant and susceptible lines. For instance, metabolomic studies demonstrated that many metabolites are modulated in resistant sunflower in response to the fungus *Sclerotinia sclerotiorum* and in resistant barley and wheat after inoculation with *Fusarium graminearum* (Jobic et al. 2007; Bollina et al. 2010; Peluffo et al. 2010; Gunnaiah et al. 2012; Kumaraswamy et al. 2012). Interestingly, these works demonstrate that a considerable proportion of the resistance is explained by the accumulation of pre-existing metabolites, such as flavonoids and phenolic acids. In addition, many other metabolites were shown to be produced in response to the pathogen, such as different sugars, organic acids, amino acids, terpenoids, and phenylpropanoids. Interestingly, infected barley plants presented elevated levels of a glycosylated form of the fungal virulence factor deoxynivalenol (DON). As it has considerable effects on the plant's secondary metabolism, conjugation of this factor toward an inactive form was proposed to be a proper detoxifying strategy (Bollina et al. 2010). In this trend, the amount of phenylpropanoids in barley is reduced in plants infected by the wild-type strain of *F. graminearum* but not in plants infected by a hypovirulent strain unable to produce DON and other trichothecenes. Moreover, the quantity of resistance-related metabolites in barley-resistant lines is higher when inoculated with the hypovirulent strain (Kumaraswamy et al. 2012). Interestingly, the resistance mechanism against *F. graminearum* in wheat seems to differ considerably. Gunnaiah et al. (2012) tried to discern the bases for resistance in this plant species making a nice integration between metabolomic and proteomic data. They found that many metabolites from the phenylpropanoid pathway were only present in the resistant line (or induced proportionally in a higher manner compared to a near-isogenic susceptible line), what was associated to the expression of some of the most important enzymes of this metabolic pathway. Finally, these authors showed that the plant cell wall was strengthened by the deposition of metabolites of this metabolic pathway. Similarly, metabolic profiling demonstrated that soluble phenylpropanoids such as sinapoyl glucosides, coniferin, syringin, and lignans are accumulated in *Arabidopsis* during the early stages of the infection by the fungus *Verticillium longisporum* (Konig et al. 2014). The participation of these metabolites in plant defense was verified by using mutant lines in this pathway. Thus, it was shown that symptoms were incremented in a mutant line unable to produce sinapoyl esters, whereas a coniferin-accumulating transgenic line was more tolerant.

Recently, Warth et al. (2015) evaluated the changes in the plant metabolome after DON treatment in six genotypes of wheat with different levels of resistance to *F. graminearum*. They found that treatment with the fungal factor produces a considerable reduction in the concentration of intermediates from glycolysis and other sugars as well as the amino acids alanine and serine. By the contrary, aromatic amino acids and biogenic amines associated to plant defense were incremented. However, as this phenomenon occurs in all tested genotypes, this work was unable to associate metabolic modifications to resistance.

Other works support the idea that amino acid metabolism may have a considerable role in plant defense. In this trend, GC-MS analysis demonstrated that priming for defense in *Arabidopsis* after root infection by *Trichoderma asperelloides* seems to be related to the activation of the amino acid metabolism in leaves (Brotman et al. 2012). Moreover, it was shown that pipercolic acid, one of the intermediate compounds of the lysine catabolic pathway, is accumulated in many plant species in response to pathogen infection. Interestingly, MS analyses demonstrated that exogenous application of pipercolic acid in *Arabidopsis* is sufficient to promote common plant defense responses such as SA and camalexin biosynthesis (Navarova et al. 2012). Recent studies also identified metabolites such as indole acetic acid, indole-3-carboxaldehyde, and camalexin as key components of the defense signaling against the necrotrophic fungus *Plectosphaerella cucumerina* in *Arabidopsis* (Gamir et al. 2014).

Samples used for omics studies in plant-microbe interactions usually consist of a mix of infected and non-infected cells, an issue that may mask actual changes in metabolite abundance and lead to erroneous interpretations of the results obtained. Even though this issue can be overcome in transcriptomic and proteomic studies with the availability of detailed genomic information of the interacting organisms, it is one of the major challenges in plant metabolomics. This is because it is very hard (if not impossible) to distinguish whether the metabolites are derived from the plant or the microorganism. Allwood et al. (2010) tackled this problem by using a plant cell-pathogen co-culture-based approach, where *Arabidopsis* cells were separated from *P. syringae* cells via differential filtering and centrifugation. Afterwards, Fourier transform infrared spectroscopy (FTIR) was conducted to analyze metabolic profiles in both organisms. Even though separation procedures are not adaptable to all plant-microbe interaction and despite the fact that these culture conditions only partially represent the real situation existing *in planta*, science will certainly benefit from studies on the interface between plants and their microbial pathogens/symbionts. For instance, the plant apoplast (the extracellular space including plant cell wall) comprises one of the first compartments where host-pathogen interactions occur. This compartment suffers remarkable changes during the pathogenic process and offers the means for delivering proteins and molecules with important roles on virulence or defense. However, just a few attempts have been made to analyze the metabolic status of the apoplastic compartment. In this trend, Floerl et al. (2012) identified the modulation in the abundance of hundreds of defense-associated metabolites in the apoplast of *Arabidopsis* in response to *V. longisporum*, such as glycosides of SA, lignans, dihydroxybenzoic acid, and oxylipins.

6.3.2 Beneficial

The changes provoked by beneficial microorganisms on the plant metabolome have not been studied in depth so far. There are, however, a few works describing the modifications in the content of primary and secondary metabolites. For instance, the metabolome of poplar plants inoculated with an endophytic strain of the endophyte *Paenibacillus* sp. was analyzed by GC-MS, which identified 11 metabolites that were consistently modified by inoculation (Scherling et al. 2009). Most of these metabolites decreased after infection, including organic acids (malate, succinate, fumarate, and citrate), amino acids (phenylalanine and oxoproline), and sugar phosphates (fructose-6-P). On the other hand, asparagine, urea, and threitol were increased in inoculated plants. These results indicate that the presence of *Paenibacillus* sp. induces the downregulation of central metabolic pathways of the plant while increases amino acid turnover. A comparable response was shown to occur in legumes during their associations with rhizobia (Prell and Poole 2006). The metabolome of *Arabidopsis* plants after inoculation with the rhizobacterium *P. fluorescens* SS101 was analyzed by an untargeted LC-MS-based approach (van de Mortel et al. 2012). In this work, the authors found 46 and 13 differentially modified metabolites in roots and leaves, respectively. The metabolites that were increased in both plant organs were mainly the glucosinolates, phytoalexin scopoletin glucoside, D-gluconate, and indole-3-carboxylic acid β -D-glucopyranosyl ester. These changes in metabolite content in Pf.SS101-inoculated plants were accompanied by the upregulation of the genes involved in their synthesis. In turn, the maize response to *P. putida* KT2440 was characterized by the accumulation of several phospholipids, particularly diacylglycerophosphocholine (Planchamp et al. 2015), whereas the benzoxazinone identified as 2-hydroxy-4,7-dimethoxy-1,4-benzoxazin-3-one glucoside was reduced considerably. These results are in agreement with previous studies analyzing the changes in secondary metabolites in maize plants under greenhouse conditions inoculated with several microorganisms, such as different strains of the PGPB *Azospirillum* spp. In this case, changes in the content of benzoxazinoids and phenolic compounds were reported to occur in a strain-dependent manner (Walker et al. 2011). Similar results were also observed in maize plants under field conditions using different combinations of the inoculants *Azospirillum lipoferum* CRT1, *P. fluorescens* F113, and *G. intraradices* JJ291 (Walker et al. 2012). More work should be conducted in order to understand the implication of these metabolites in the interaction of plants with beneficial microbes.

6.4 Perspectives

Bit by bit, modern science has made a remarkable progress in the understanding on how plant and microbes communicate with each other. Thus, a broad spectrum of the repertory of molecules sensed by plants to recognize microorganisms has been discovered. We should add to this list thousands of genes activated and chemicals synthesized afterwards to hinder pathogen attack or facilitate the infection by

beneficial microorganisms, as well as myriad virulence components produced by microorganisms to clear a path through plant defensive responses. In addition, our knowledge on the regulatory mechanisms that governs the production of these molecules is growing exponentially. Undoubtedly, a large part of the progress in this field is due to the development of reliable omics approaches. Even though we have only reviewed transcriptomics and metabolomics in this chapter, proteomics has made a tremendous contribution to this research area. Table 6.1 shows a brief summary of some of the most relevant proteomic works.

Table 6.1 Summary of some relevant works studying the changes of the plant proteome during plant-microbe interactions

Plant	Interaction	Comparison or treatment	References
<i>Arabidopsis</i>	Pathogenic	<i>P. syringae</i> pv. tomato DC3000	Jones et al. (2004)
<i>Arabidopsis</i>	Pathogenic	<i>P. syringae</i> pv. tomato DC3000	Jones et al. (2006)
<i>Lycopersicon hirsutum</i>	Pathogenic	<i>Clavibacter michiganensis</i> subsp. <i>michiganensis</i>	Coaker et al. (2004)
<i>Oryza sativa</i>	Pathogenic	Compatible and incompatible races of <i>Xanthomonas oryzae</i> pv. <i>oryzae</i>	Mahmood et al. (2006)
<i>Oryza sativa</i>	Pathogenic	<i>Xanthomonas oryzae</i> pv. <i>oryzae</i> infection	Chen et al. (2007)
<i>Nicotiana occidentalis</i>	Pathogenic	' <i>Candidatus Phytoplasma mali</i> ' strain AT	Luge et al. (2014)
<i>Actinidia chinensis</i>	Pathogenic	<i>P. syringae</i> pv. <i>actinidiae</i>	Petriccione et al. (2013)
<i>Actinidia deliciosa</i>	Pathogenic	<i>P. syringae</i> pv. <i>actinidiae</i>	Petriccione et al. (2014)
<i>Glycine max</i> [L.] Merr. cv. Akishirome	Symbiotic	Nodule mitochondria vs. root mitochondria	Hoa et al. (2004)
<i>Glycine max</i> cv. Stevens	Symbiotic	Soybean peribacteroid membrane-specific proteins	Panter et al. (2000)
<i>Glycine max</i> [L.] Merr, cv. Williams 82	Symbiotic	Inoculated vs. uninoculated (<i>Bradyrhizobium japonicum</i>) root hairs	Wan et al. (2005)
<i>Melilotus alba</i>	Symbiotic	Nodule vs. root	Natera et al. (2000)
<i>Medicago truncatula</i>	Symbiotic	Ethylene-insensitive mutant vs. wild-type after <i>Sinorhizobium</i>	Prayitno et al. (2006)
<i>Medicago truncatula</i>	Symbiotic	<i>Sinorhizobium meliloti</i>	Schenkluhn et al. (2010)
<i>Oryza sativa</i>	Endophytic	<i>Azoarcus</i> sp. strain BH72	Miché et al. (2006)
<i>Vigna unguiculata</i>	Symbiotic	Root hairs inoculated with wild-type <i>Rhizobium</i> sp. NGR234 vs. hair-deformation minus mutants	Krause and Broughton (1992)
<i>Arabidopsis</i>	Symbiotic	Volatiles organic compounds from the rhizobacterium <i>Bacillus subtilis</i> GB03	Kwon et al. (2010)

Nevertheless, the entire interplay between these organisms is still far from being fully elucidated. For instance, the roles played by numerous regulated genes and metabolites overproduced during plant immune responses are unknown. There is also a lack of information in the regulatory mechanisms that operate on important genes, the relationship between the activation of known defense mechanisms with other metabolic pathways, and the responses elicited in a vast amount of non-model plant species. At last, we only have a glimpse of the contribution of metabolites produced by microorganisms in the outcome of their interactions with plants.

More advances in this direction will be prompted by the advent of new tools able to analyze these components right in the interface between plants and microbes, while they are establishing associations as it occurs in nature. This must be accompanied by a deeper exploration of the defense mechanisms activated in model and non-model plants as well as the virulence activity of different strains of microorganisms. This goal may be addressed by a combination of different omics approaches, which will lead in the future to a thorough comprehension of plant immunity and provide us with the key to improve plant protection and productivity.

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