REVIEW

Systems understanding of plant–pathogen interactions through genome-wide protein–protein interaction networks

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Abstract Plants are frequently affected by pathogen infections. To effectively defend against such infections, two major modes of innate immunity have evolved in plants; pathogen-associated molecular pattern-triggered immunity and effector-triggered immunity. Although the molecular components as well as the corresponding pathways involved in these two processes have been identified, many aspects of the molecular mechanisms of the plant immune system remain elusive. Recently, the rapid development of omics techniques (e.g., genomics, proteomics and transcriptomics) has provided a great opportunity to explore plant–pathogen interactions from a systems perspective and studies on protein–protein interactions (PPIs) between plants and pathogens have been carried out and characterized at the network level. In this review, we introduce experimental and computational identification methods of PPIs, popular PPI network analysis approaches, and existing bioinformatics resources/tools related to PPIs. Then, we focus on reviewing the progress in genome-wide PPI networks related to plant–pathogen interactions, including pathogen-centric PPI networks, plant-centric PPI networks and interspecies PPI networks between plants and pathogens. We anticipate genome-wide PPI network analysis will provide a clearer understanding of plant–pathogen interactions and will offer some new opportunities for crop protection and improvement.

Keywords plant–pathogen interactions, systems biology, omics, plant immunity, protein–protein interaction, network

1 Introduction

Plant pathogens, including bacteria, fungi, oomycetes and viruses, can cause diseases and epidemics that greatly affect agricultural production and food security all over the world[1]. Historically, a series of recurring disastrous events was related to devastating plant diseases, which significantly affected human life and civilization[1–3]. The most frequently mentioned event is the Great Irish Famine from 1845 to 1852. Potato blight caused by *Phytophthora infestans* eradicated the potato crop, which reduced the Irish population by a quarter, leading to starvation, death and forced migration[2]. In 2000, the yellow rust on wheat caused by *Puccinia striiformis* spread across the United States and triggered a reduction in wheat production[3]. Even with the applications of modern crop protection strategies, approximately 15% of global crop production was lost due to diverse plant diseases[1]. Therefore, plant–pathogen interaction is a long-standing research topic in agriculture science, which may provide better strategies for crop protection and improvement.

The interactions between plants and pathogens involve bidirectional recognition. On the one hand, plants need to sense the foreign molecules delivered by pathogens to activate the plant innate immunity. On the other hand, pathogens need to identify special target proteins to disrupt the plant immune system. It has been well established that the plant innate immunity consists of two major modes, i.e., pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI)[4,5] (Fig. 1). PAMPs are conserved molecules and considered to be critical for the survival of pathogens. Pattern recognition receptors (PRRs) located on plant plasma membranes perceive PAMPs to trigger PTI, which can repel most invading pathogens. To decipher the PTI process, attention has been paid to the detection of PAMP-PRR interactions and some key PRRs and the corresponding PAMPs have been identified[6].

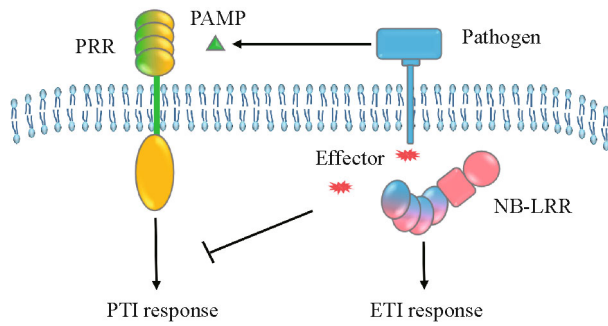To overcome the PTI and dampen plant basal defenses,

Fig. 1 Two major plant innate immune modes; pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI). Pattern recognition receptors (PRRs) are plant proteins present on plasma membranes. Once PRRs sense PAMPs, PTI will be activated. To interfere with PTI, pathogens secrete effectors into plant cells. Nucleotide binding/leucine-rich-repeat (NB-LRR) proteins can recognize effectors to initiate ETI.

pathogens have evolved to produce effectors, some of which enter plant cells through secretion systems[7] (Fig. 1). In response, resistance (*R*) genes, which recognize effectors and activate ETI, have evolved in plants. Nucleotide binding/leucine-rich-repeat (NB-LRR) proteins encoded by *R* genes contain an N-terminal nucleotide binding domain and C-terminal leucine-rich-repeat domain, and they monitor effectors in three ways[8]. The first way is the direct interactions between NB-LRRs and effectors. Once plant NB-LRR proteins sense pathogen effectors, the ETI is triggered. The second and third ways are the indirect interactions between NB-LRRs and effectors. In the second way, NB-LRRs monitor the target proteins of effectors. When effectors attempt to attack the plant target proteins, which are important factors in the plant immune defense, NB-LRRs act as guards and they can sense the signal to activate the ETI. The third way is the plant decoy strategy in which plants employ decoy proteins irrelevant to immunity but structurally related to defense components to trap effectors. As described in the second way, decoy proteins bound to and monitored by NB-LRR can also trigger ETI when their state is changed[4,9].

Over recent decades, there have been many advances in the understanding of plant–pathogen interaction. The identification of the molecular components as well as the corresponding pathways has provided a relatively clear understanding of plant immune system. In particular, the study of plant–pathogen interactions has also been stimulated by the emergence of various omics techniques, such as genomics, proteomics and transcriptomics. Of these, genomics is particularly important and lays the foundation for the development of other omics techniques. With the rapid development of next-generation sequencing (NGS) technique, numerous plant and pathogen genomes have been fully sequenced. Proteomics is a key technique for the analysis of the proteins involved in plant–pathogen

interactions[10]. Transcriptomics is also important to investigate plant–pathogen interactions, and has been employed to learn how plants respond to the pathogen invasion and how pathogens counter the plant defense at the transcript level[11]. DNA microarray and RNA sequencing are two major transcriptomics techniques for acquiring the expression profile of genes on a large scale. Plant–pathogen interactions are sophisticated and dynamic in the continually evolving competition between pathogens and plants. When plants respond to biotic stress, a series of biological processes rather than a single gene or protein will be change. Therefore, it is necessary to explore plant–pathogen interactions from a systems perspective (e.g., network level[12]). With the availability of huge amounts of omics data generated from high-throughput omics techniques, network interactions have become a powerful approach to further decipher the molecular mechanisms of plant–pathogen interactions through network biology.

In network biology, complex systems are modeled as networks whose components are denoted as nodes and the relationships among them are defined as edges or links. A variety of biological systems have been investigated through network analysis, including protein–protein interaction (PPI) networks, metabolic networks, gene co-expression networks, and regulatory networks[13]. In this review, we only focus on the construction and analysis of PPI networks related to the complex interactions between plants and pathogens. We first introduce the basic definitions and properties of PPI networks, including the experimental determination and prediction methods of PPIs, the network analyses related to PPI networks, and the major aspects of the application of PPI networks. Then, we focus on reviewing the current progress and challenges of PPI networks toward a better understanding of plant–pathogen interactions.

2   Methods for constructing PPI networks

2.1   Basic definitions and properties of PPI networks

Protein interactions are fundamental to most biological processes and can be presented as a network (also known as interactome) to investigate complex biological systems. In a PPI network (Fig. 2a), nodes and edges are basic elements, in which each node represents a protein and each edge represents a physical interaction between a protein pair. The PPI network can be compiled from experimentally determined or predicted PPIs. The development of some high-throughput experimental methods has dramatically accelerated genome-wide PPI network construction.

To provide a global understanding of a PPI network, network topology analysis is necessary and it can be carried out at different levels. At the node level, several parameters have been proposed to describe the network topology, such as network degree, clustering coefficient,

closeness centrality, and betweenness centrality[14]. As with other biological networks, the PPI networks have been characterized as scale-free, in which most nodes have low degrees and a small percentage of nodes have high degrees[15,16]. The proteins with high degrees are often called hubs, which tend to perform more important functional roles than non-hub proteins. Hubs are further classified as date and party hubs (Fig. 2b). Date hubs display low expression correlations with their partners, while party hubs are often highly co-expressed with their partners[15].

The PPI networks can be analyzed at the module level (Fig. 2c). In general, a module is defined as a cluster of physically or functionally related nodes that are assembled together to perform a specific function[14]. Nevertheless, modules are not static and they change or disappear across different conditions[17]. In a PPI network, different modules act synergetically to perform cellular functions. Therefore, investigating how modules in PPI networks interact with each other is a valuable starting point in understanding the formation of phenotypes from a systems perspective. The detection of modules is crucial for network analysis. Various clustering methods (Table 1), such as Markov Cluster Algorithm (MCL), CFinder[18], MCODE[19] and ClusterONE[20], have been developed to address this task. Although the underlying algorithm of each clustering method may be distinct, they have been successfully applied to the discovery of modules in PPI networks.

PPI networks have been widely used to address diverse biological questions. A typical application is to infer biological function for unknown proteins, i.e., the so-called "guilt-by-association" strategy. The central idea of "guilt-by-association" is that interacting proteins tend to share similar biological function[21] and it has been applied to improve functional annotation of proteins from different species, including yeast[22] and *Arabidopsis*[23]. Moreover, it is also possible to prioritize disease candidate proteins in PPI networks upon the "guilt-by-association" principle[24,25].

2.2　Experimental determination of PPIs

Protein interactions can be measured using different experimental techniques. Some high-throughput techniques allow identification of a large number of PPIs in a cell, such as yeast two-hybrid screening (Y2H), tandem-affinity purification coupled with mass spectrometry (TAP-MS) and protein microarray. The working principles, detailed procedures, advantages and limitations of these techniques have been reviewed extensively[26–29]. Therefore, only the basic concepts of some popular techniques are covered here.

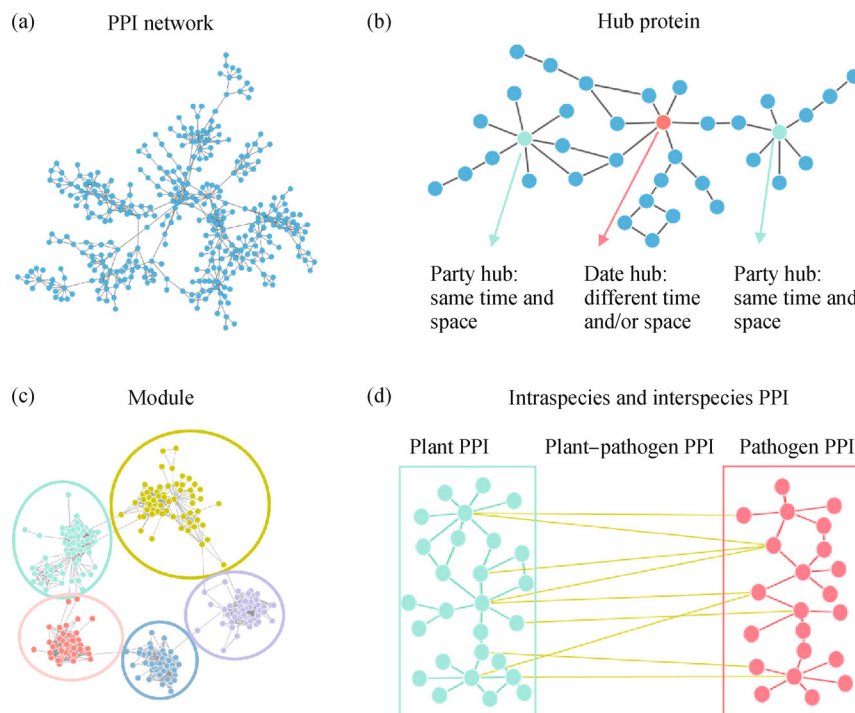Y2H is an *in vivo* PPI determination technique. Briefly,

Fig. 2　Introduction to pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) network. (a) Each node represents a protein and each edge represents an interaction between two proteins; (b) date hubs exhibit low co-expression with their interacting partners (i.e., interact with partners at different time and/or space), while party hubs tend to highly co-express with their partners (i.e., co-expression at the same time and space); (c) a PPI network is divided into five modules, which are marked in different colors; (d) plant PPIs are shown using green edges, pathogen PPIs are shown using red edges, while plant–pathogen PPIs are shown using yellow edges.

Table 1 Bioinformatics tools and resources related to plant–pathogen interactions

Name	Description	URL
Keyword: network clustering algorithm		
MCL	Fast and scalable unsupervised clustering algorithm based on simulation of flow	http://micans.org/mcl
CFinder	Fast and efficient clustering algorithm based on the Clique Percolation Method	http://cfinder.org
MCODE	Well-known automated clustering algorithm to find highly interconnected subgraphs	http://baderlab.org/Software/MCODE
ClusterONE	A graph clustering algorithm that readily generates overlapping clusters	http://paccanarolab.org/clusterone
Keyword: cytoscape and its plugin		
Cytoscape	An open source software tool for integrating, visualizing, and analyzing data in the context of networks	http://www.cytoscape.org
BiNGO	GO enrichment analysis plugin	http://apps.cytoscape.org
ClueGO	GO enrichment analysis plugin	http://apps.cytoscape.org
GeneMANIA	Gene function prediction plugin	http://apps.cytoscape.org
ReactomeFIPlugIn	Pathway analysis plugin	http://apps.cytoscape.org
KEGGscape	Pathway analysis plugin	http://apps.cytoscape.org
clusterMaker	An integrative cluster plugin	http://apps.cytoscape.org
Keyword: database		
BioGRID	A comprehensive database containing plant PPI	http://www.thebiogrid.org
IntAct	A comprehensive database containing plant and plant–pathogen PPI	http://www.ebi.ac.uk/intact
TAIR	An integrated *Arabidopsis* database containing PPI	http://www.arabidopsis.org
Arabidopsis Interactome Network Map	A proteome-wide binary protein–protein interaction map for *Arabidopsis*	http://interactome.dfci.harvard.edu/A_thaliana
AtPID	*Arabidopsis* protein interactome database	http://www.megabionet.org/atpid/webfile
ANAP	An integrated PPI database for *Arabidopsis*	http://gmdd.shgmo.org/Computational-Biology/ANAP
PHI-base	Plant–pathogen PPI database	http://www.phi-base.org
PRIN	A predicted rice PPI network	http://bis.zju.edu.cn/prin
AraNet	*Arabidopsis* functional gene network	http://www.functionalnet.org/aranet
AraONE	A genome-wide *Arabidopsis* gene network	http://systbio.cau.edu.cn/pinet/home.php
PPIN-1	A plant–pathogen immune network	http://signal.salk.edu/interactome/PPIN1.html
PPIRA	*R. solanacearum–Arabidopsis* PPI network	http://protein.cau.edu.cn/ppira

in a Y2H experiment, a protein of interest is genetically fused to a DNA binding domain, while another protein is genetically fused to a transcriptional activation domain[27]. In case of a physical interaction between the protein pair, a functional transcription factor will be reestablished, resulting in the expression of a reporter gene. Otherwise, the reporter gene remains inactive. Y2H has been widely used in PPI measurements with the scales ranging from individual proteins to whole proteomes.

TAP-MS involves the combination of affinity purification and mass spectrometry (MS), which is also a powerful method of studying PPIs *in vitro*. In a TAP-MS assay, a protein of interest will be fused to an affinity tag for *in vivo*

expression. The multiple-component protein complex can be directly isolated from the cell lysate through affinity purification steps and further processed by a downstream MS method[26]. The core idea of the MS method is to produce ions that can be detected based on their mass-to-charge ratios, thus allowing the identification of protein sequences[28]. With the assistance of some algorithms, finally, the search of mass spectra against known protein sequence databases will identify the candidate proteins involved in the interaction.

Protein arrays also provide great prospects for high-throughput measurement of PPIs. To prepare protein arrays, proteins are immobilized on the surface of glass

slides. This allows the detection of PPIs using fluorescent or chemiluminescent probes[29]. Most existing protein arrays are prepared by spotting recombinant proteins purified from heterologous systems[27]. As a promising alternative, the nucleic acid programmable protein array has also been developed, which has been used to validate plant interactome mapping[27,30].

2.3   Computational prediction of PPIs

Considering that the experimental methods are relatively expensive, time consuming, and labor intensive, a plethora of prediction methods have been developed to complement the experimental methods in recent years[31]. The prediction methods can be roughly grouped into three categories. The first group relies on protein sequence/domain similarity to conduct the PPI prediction. Representative methods include the interolog method[32] and the domain-based method[33]. The interolog method can be described as the transfer of PPI annotations between species. Briefly, two proteins can be predicted to interact with each other if an experimentally verified interaction exists between their respective homologous proteins in another organism. The domain-based method uses domain interaction information, which is derived from known protein 3D complex structures, to infer the potential PPIs. If two proteins contain an interacting domain pair, we can foretell that these two proteins have a high chance to interact with each other[34]. The second group relies on the observed evolutionary or functional relationship of interacting proteins to predict PPIs. In general, this type of methods is more likely to infer functionally associated protein pairs, rather than physical interactions. The third category uses machine learning methods to predict PPIs based on features extracted from protein sequences.

In general, the false positive rates derived from the aforementioned prediction methods are still high, meaning that there is much room for improvement. Indeed, some novel prediction methods have been continuously developed by employing state-of-the-art prediction algorithms, designing new computational frameworks, and incorporating more sequence/structural features[35,36]. Regarding the genome-wide PPI network construction, it should be emphasized that the interolog method and domain-based method are favored and widely applied, probably due to the fact that these two methods have clear prediction principles and can be easily implemented.

2.4   Existing visualization tools and databases

Network visualization is becoming an integral part of the process of network analysis, which has significantly promoted the development of systems biology. Typically, an excellent visualization tool not only intuitively presents the network organization, but also can perform essential computational analyses. One of the most popular tools is Cytoscape (http://www.cytoscape.org) (Table 1), which is a state-of-the-art and comprehensive network visualization platform and allows expression profiles as well as other molecular states to be integrated into networks. To satisfy different purposes, a wide range of Cytoscape plugins are available at http://apps.cytoscape.org. For example, the plugins of BiNGO[37] and ClueGO[38] can be used for the GO enrichment analysis; GeneMANIA[39] can bring fast gene function prediction; and ReactomeFIPlugIn[40] as well as KEGGscape[41] can perform the pathway analysis. Clustering is sometimes a prerequisite to analyze the network, and the clusterMaker plugin[42] that integrates multiple clustering algorithms including MCODE[19] and MCL is also available in Cytoscape.

To store and manage the increasingly large amount of available PPI data, some well-maintained PPI databases have been established (Table 1), which can be divided into generic and species-specific databases. BioGRID (http://www.thebiogrid.org)[43] and IntAct (http://www.ebi.ac.uk/intact)[44] are two renowned generic PPI databases. Both of them collect PPIs from the literature curation and include PPIs from any species. In contrast, some PPI databases are species specific. For example, The *Arabidopsis* Information Resource (TAIR; http://www.arabidopsis.org)[45] is the main repository of *Arabidopsis* data including PPIs; the Pathogen-Host Interaction database (PHI-base; http://www.phi-base.org)[46] may be a good choice to obtain plant–pathogen interactions.

3   Understanding plant–pathogen interaction through PPI networks

Depending on the research focus in plant–pathogen interactions, the PPI networks under investigation can be grouped into three types, including pathogen-centric PPI networks, plant-centric PPI networks and interspecies PPI networks (Fig. 2d). Pathogen-centric PPI networks can reflect the lifestyles of different pathogens, and thus provide further understanding of pathogen pathogenicity. Plant-centric PPI networks are generally helpful to provide comprehensive understanding of plant immune responses. Comparatively, the interspecies PPI networks are more directly involved in the competitive interaction between plant and pathogens. We will review the current research status of these three types of PPI networks in the following subsections.

3.1   Construction and analysis of pathogen-centric PPI networks

Although the genomes of many plant pathogens have been sequenced, the experimentally determined PPIs are still limited. To analyze PPIs from a systems perspective, genome-wide prediction of PPI networks has been conducted in several plant pathogens, including *Magna-*

porthe grisea[47], *Fusarium graminearum*[48,49], *Rhizocto-nia solani*[50] and *Xanthomonas oryzae* pv. *oryzae* (*Xoo*)[51].

In 2008, we started a study to predict the PPI network of *M. grisea*[47], which is a fungal pathogen causing the most severe disease of rice. Based on the interolog method, 11674 predicted PPIs among 3017 *M. grisea* proteins were inferred from known PPIs of five model organisms. We further assessed the reliability of the whole PPI network through indirect computational methods. Compared with randomized PPI networks, we found the PPIs in the predicted network tended to share similar GO annotations, contain known DDIs, and have correlated gene expression patterns. To analyze the established PPI network, we collected 100 pathogenicity proteins encoded by pathogenicity genes from the PHI-base and published literature. We found that 32 pathogenicity proteins existed in the predicted PPI network. The degrees of the 32 pathogenicity proteins were higher than other proteins in the predicted PPI network, which conformed to the viewpoint that important proteins have more interacting partners[52].

Similar work aimed at PPI network prediction for the bacterial pathogen *Xoo* strain PXO99^A has also been reported[53]. To explore the pathogenic mechanisms of *Xoo* PXO99^A, Guo et al. applied the interolog and modified domain-based[54] methods, and predicted 36886 PPIs among 1988 *Xoo* PXO99^A proteins. The *K*-nearest neighbor classification[55] and GO annotation methods demonstrated the reliability of the predicted PPI network. Like other biological networks, the *Xoo* PXO99^A PPI network was also characterized as a scale-free network. Subsequently, σ factors, flagellar and chemotaxis systems, and signal transduction subnetworks were extracted from the predicted PPI network and these subnetworks were focused on to study the pathogenic mechanisms of *Xoo* PXO99^A. They found that σ^28 and σ^54 factors could be involved in the flagellar synthesis and motility of *Xoo* PXO99^A, and transcription factors RpoA, RpoB and RpoC set up a bridge to connect σ^28 and σ^54 factors in this process. Moreover, they speculated that the cAMP and cyclic diguanosine monophosphate pathways which were significant for pathogenic bacteria also existed in *Xoo* PXO99^A.

In general, the predicted PPI networks can enhance our global understanding of pathogenic mechanisms of the corresponding pathogens and can have some potential applications, although they are far from complete and certainly contain many false positives. First, the predicted networks are useful in investigating many functional unknown proteins in pathogens. Second, the modules containing known pathogenicity genes can be detected, which may be useful for identifying new pathogenicity genes[47]. Last but not least, the predicted PPI network will be further employed to guide the experimental design of future high-throughput PPI mapping efforts.

3.2 Construction and analysis of plant-centric PPI networks

Compared with the established plant–pathogen PPI networks, plant PPI networks have been more intensively studied due to their important roles in deciphering plant gene functions. Both experimental and computational methods have been intensively employed to chart the plant interactome[30,56–58]. Based on an improved Y2H system, *Arabidopsis* Interactome Mapping Consortium (2011) reported the first systematic proteome-wide binary PPI map of *Arabidopsis*, which covered about 6200 highly reliable interactions among 2700 proteins[30]. Indeed, these data had doubled the number of known PPIs of *Arabidopsis* and could provide functional hypotheses for the functions of many previously unidentified proteins. Although the high-throughput experimental technologies have been applied in the plant kingdom, the available PPI data are still limited in comparison to the hundreds of thousands of PPIs that occur in a plant cell. To narrow down this number, computational methods have also been employed to help the construction of PPI networks in plants.

Geisler-Lee et al. reported an interactome[59] for *Arabidopsis* predicted from interacting orthologs in four model organisms (i.e., yeast, nematode, fruit fly and human). Based on the amount of supporting evidence, a confidence score for each predicted interaction was assigned as a quality control. The predicted interactome contained approximately 20000 interactions with different confident levels for 3617 *Arabidopsis* proteins. Lin et al. employed a Support Vector Machine classifier to predict potential *Arabidopsis* PPIs based on a variety of features[60]. It was estimated that the predicted interactions could cover approximately 30% of the entire interactome with reasonable precision. Comprehensive PPI networks have also been constructed in some important crops. For instance, the 76585 rice PPIs of the Predicted Rice Interactome Network (PRIN) resource were deduced from their interologs in yeast, nematode, fruit fly, human, *Escherichia coli* and *Arabidopsis* through the InParanoid algorithm[61].

To facilitate the work of the research community, some plant-specific PPI databases have been established to organize and store PPI data. One example is AtPID (http://www.megabionet.org/atpid/webfile[62];), which contains curated and predicted interaction data. The predicted PPI data were inferred from interologs, microarray profiles, GO annotation, known interacting domains and genome contexts. This database covered 28062 PPI pairs, including 23396 pairs generated from prediction methods, 3866 pairs collected from the literature, and 800 pairs inferred from enzyme complexes in KEGG (http://www.genome.jp/kegg). ANAP (*Arabidopsis* Network Analysis Pipeline; http://gmdd.shgmo.org/Computational-Biology/ANAP[63];) integrates 11 *Arabidopsis* protein interaction databases, covering more than 200000 unique protein interaction

pairs. ANAP provides a user-friendly graphical interface that can allow easy and intuitive network visualization. It also offers extensive detailed evidence for each interaction.

In plants, some comprehensive gene co-function networks have also been constructed in which PPI data are often included. For instance, Lee et al. integrated diverse omics data into a genome-wide *Arabidopsis* functional gene network called AraNet, which contains more than one million functional associations among 19647 genes[64]. It should be emphasized that these established plant PPI-related networks have been important data resources to investigate plant immune response against the infection by pathogens, although they were not specifically constructed for this task.

Very recently, we constructed a genome-wide *Arabidopsis* gene network called AraONE to study plant immune responses against pathogen infections[65] (Fig. 3). AraONE is an integrated gene network, which combines mainly experimental PPIs, confirmed protein-DNA binding data, and the co-expression relationships between transcription factors and targets. We also collected *Arabidopsis* gene mRNA microarray data corresponding to two different immune responses (PTI and ETI) and control condition from public databases. Using the microarray data and the established gene network as input, the Network-Guided Forest (NGF) algorithm was further used to identify key genes/interactions involved in the immune response. Note that NGF is an improved Random Forest method, a powerful machine learning algorithm that employs many different decision trees to infer the classification model[66]. Compared with classical Random Forest, the network topology information is introduced in the NGF algorithm to supervise the growth of each decision tree. Moreover, we performed comprehensive network analyses to obtain a global understanding of the *Arabidopsis* immune response. In particular, at the whole network level, we identified immune response-related network modules and examined the organization structures of these modules in PTI and ETI. Notably, we found the defense modules in ETI formed relatively independent structures, which could reflect the evolutionary demands for a rapid and stable immune response[65].

3.3 Construction and analysis of plant–pathogen PPI networks

In comparison to plant or pathogen PPI networks, the interspecies PPI networks between plants and pathogens are more directly involved in plant–pathogen interactions. In the past several years, studies of such types of networks have been initiated[67,68]. Mukhtar et al. analyzed plant–pathogen interactions by constructing an experimentally identified interspecific PPI network (PPIN-1 in Table 1), which contained 3148 interactions between the effectors of pathogens (Gram-negative bacterium *Pseudomonas syringae* and obligate biotrophic oomycete *Hyaloperonospora arabidopsidis*), the effector target proteins in *Arabidopsis* and other *Arabidopsis* immune proteins[68]. They assumed that the effectors from evolutionarily diverse pathogens targeted the same defense-related proteins in plants. To test this hypothesis, they extracted 165 *Arabidopsis* proteins directly targeted by effectors, and found that 18 proteins were commonly targeted by both *P. syringae* and *H. arabidopsidis,* which was significantly larger than the common ones resulting from random experiments. Thus, the observation supported the idea that pathogen effectors were inclined to target a limited set of plant target proteins. Through further network topology analysis, they also found that the target proteins of effectors own more interaction partners (higher degree) compared with other *Arabidopsis* proteins. This indicated that pathogen effectors tended to attack hubs to disrupt immune system, which has been extensively demonstrated in human–virus interaction networks[69,70].

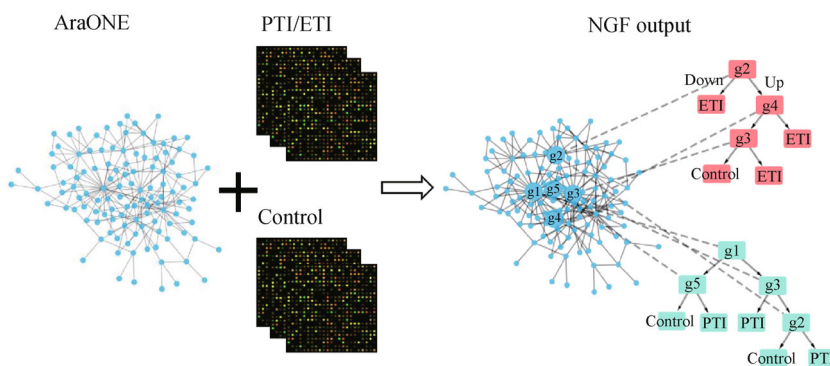Comparatively, the interspecific PPIs between plants and pathogens are rare. In this context, a series of computa-

Fig. 3 Methodological overview of the integration of AraONE and plant immunity-related transcriptomics data. Using the PTI/ETI gene expression profiles and the integrated gene network (i.e., AraONE) as input, the NGF algorithm is used to train classification models for distinguishing different microarray data. Based on the trained classification models, key genes/interactions involved in the plant immune response can be inferred, which are further used to provide insights into the gene network organizations of PTI and ETI.

tional studies has been initiated to predict plant–pathogen interactions[51,71,72], although the web servers of these prediction methods are still not available to the research community. In 2012, we conducted the prediction of PPIs between *Ralstonia solanacearum* and *Arabidopsis*, and compiled the predicted interspecies PPIs into a network called PPIRA[71]. The PPIRA network includes 3074 PPIs between 119 *R. solanacearum* proteins and 1442 *Arabidopsis* proteins. All PPIs in the network were predicted by using the interolog and the domain-based methods. We further analyzed the *R. solanacearum–Arabidopsis* interactions and found that an *R. solanacearum* protein could target 26 *Arabidopsis* proteins on average. In contrast, an *Arabidopsis* protein only interacted with two *R. solanacearum* proteins on average, which possibly explained why pathogens could infect a whole plant just through a few pathogen proteins[73]. Likewise, this phenomenon was also observed in *X. oryzae–Oryza sativa* interactions[51]. Moreover, to better understand the *R. solanacearum–Arabidopsis* interactions, we collected a further 4660 experimentally identified *Arabidopsis* PPIs from public PPI databases. CFinder was used to detect modules from these *Arabidopsis* PPIs. Of the 83 modules obtained, 22 modules were defined as pathogen-targeted modules containing at least one *R. solanacearum*-targeted protein and significantly annotated with cell cycle, channel activity and regulation of cellular metabolic processes. Moreover, three proteins of the 52 *R. solanacearum*-targeted proteins found in these 22 modules occurred in more than one module and connected different cellular processes, and these three proteins could be regarded as the bottleneck of the network. These observations implied that pathogens perhaps infected plants by attacking the bottleneck of plant networks.

The current interspecies PPI prediction method is still in its infancy. Compared with intraspecies PPI prediction, it may inevitably contain a higher false positive rate. Regarding the future methodology development, three opportunities have been identified. (1) Developing the machine learning based predictors, since the experimentally validated interspecies PPI data between plants and pathogens are accumulating. (2) Focusing on the PPI prediction between pathogen effectors and target proteins in plants, which may simplify the interspecies prediction to some extent. Recently, some state-of-the-art effector predictors have been developed, which indeed set up a good starting point for further prediction of effector targets in host plants. (3) Applying new algorithms proposed for predicting human–bacterial pathogen PPIs over the past few years[74] to the plant–pathogen interaction system.

4 Conclusions and future perspectives

Despite the remarkable progress in the field of plant functional genomics, our understanding of the many fundamental molecular mechanisms governing plant–pathogen interactions remains inadequate. With the advent of the era of 'Big Data', there is an increasing realization in the plant pathology community of the need to investigate plant–pathogen interactions through network biology. In this paper, we have reviewed research progress toward systems understanding of plant–pathogen interactions in terms of PPI networks. The current PPI network-related studies not only allow us to obtain a global understanding of pathogen pathogenicity and plant defense responses, but also provide many candidate genes with potentially crucial functions in plant–pathogen interactions[75], which deserve further experimental validation. The following are important challenges to be addressed.

Compared with the binary PPI information, the detailed 3D structural information of PPIs (termed as structural interactome) is increasingly important for the community[76]. Currently, the experimentally resolved 3D structures of PPIs between plants and pathogens are very limited, which constrains the construction of a structural interactome between plants and pathogens at a reasonable scale. With the increasingly-available protein complex structures, a large-scale structural interactome between plants and pathogens will be constructed in the future, which will undoubtedly allow researchers to investigate plant–pathogen interactions at a higher resolution.

Integration of more data into PPI network is also an efficient strategy. For instance, it has been well established that plant endogenous microRNAs[77] and protein post-translational modifications (e.g., phosphorylation[78] and ubiquitination[79]) are also heavily involved in regulating plant–pathogen interactions. To integrate these data into PPI networks, new methodologies need to be developed.

The established PPI networks can generally be regarded as static networks. However, the plant immune response is a highly dynamic process. Upon pathogen recognition, the plant cell undergoes an extensive transcriptional reprogramming in a highly dynamic and temporally regulated manner[80]. Dynamic behavioral information about the PPI network between plants and pathogens is likely to be crucial for deciphering the molecular mechanisms of plant immunity. To this end, integrating time course expression data into the PPI network would be a useful strategy to characterize the dynamics of plant–pathogen interactions[65].

In addition to PPI networks, other molecular networks (e.g., co-expression, regulatory and signaling networks) are equally important to decipher plant–pathogen interactions. Undoubtedly, different network analysis and modeling tools are required when dealing with diverse networks. Last but not least, the current systems biology studies are mainly focused on the model plant–pathogen interaction systems. Therefore, finding ways to transfer the knowledge obtained from model systems to crop protection and improvement is an urgent and challenging task.

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