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Proteomics in plant pathology: A tool for disease management

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Abstract

In present situation the major concern is to increase the productivity of the major crops and vegetables in order to meet the demand of global food supply of the constantly rising population from the limited agricultural land available. However, along with the land availability there are several other factors as well that contribute equally to the reduction in the annual productivity of the crops, among which weeds, diseases, insects and abiotic stresses are the major ones. In the field of plant pathology, the main area of research includes the losses that occur due to several pathogens which ultimately account for huge crop loss. So, in order to tackle this problem several advanced biotechnological approaches were used in recent past among which proteomics a systems biology approach is most promising. Proteomics in combination with transcriptomics, genomics and several other advanced fields yields many valuable and informative data that can be used to understand the complex interaction lying underneath in the plant-pathogen interaction. Better understanding of the pathogen virulence, mode of infection and downstream disease signaling mechanism in turn will help to design effective strategies to develop resistant cultivars which can better cope up against the attack of pathogens.

Keywords: Proteomics, transcriptomics, genomics, virulence

1. Introduction

With the discovery of proteomics science, a huge amount of progress has been made in this field, further combining proteomics science with bioinformatics and several other inter-related disciplines has reportedly increased its ability to procure useful and reliable data. Proteomics is a systems biology approach and is becoming very useful for deciphering the complex biological processes and now days it is used in several fields according to the needs of the researcher to find out valuable information. One of such use of proteomics science is in the field of plant pathology to find out the mode of infection, host- pathogen interaction and regulatory elements *viz.* transcription factors or mediators involved in the downstream signaling pathway for establishment of the disease (Kav *et al.*, 2007; Fernandez and Novo, 2012) [41, 33]. A better understanding of the mechanism of disease development is essential to generate suitable resistant cultivars which can overcome the challenge imposed by the pathogens. It has been estimated that diseases, insects and weeds altogether cause 42% losses to all crops produced worldwide (Agrios, 2005) [4]. The losses are usually lower in the developed countries and higher in the developing countries which in turn needs food the most. It has been estimated that of the 36.5% average of total losses, 14.1% are caused by diseases, 10.2% by insects and 12.2% by weeds. With 14.1% of total losses due to plant diseases alone, the total annual worldwide crop loss from plant diseases is estimated around \$220 billion (Anonymous, 2016) [6]. Hence, in order to meet the need of global food supply it is essential to have a profound knowledge about the most important pathogens and the way they infect the plants which in turn will help to prevent their spread and ultimately leads to increase in the average yield of the crop. This review would briefly cover the progress of proteomics that has been made in past decade in the field of plant pathology for the better understanding of the pathogens and their mode of infection in agriculturally important crops.

2. Role of proteomics in plant disease management

Proteomics a systems biology approach is considered as a logical choice for investigating the plant pathogen interactions. Many initial approaches for investigation were based upon two dimensional gel electrophoresis which is a good choice for rapidly identifying major proteome differences in healthy versus inoculated plants (Rampitsch and Bykova, 2012) [64].

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Plant pathogens are either viruses (including viroids, virus-like organisms and satellites), bacteria (including phytoplasmas), fungi, oomycetes, protozoans, nematodes or in rare cases parasitic higher plants. However, the majority, and most destructive, are fungi and oomycetes (Latijnhouwers *et al.*, 2003) [45]. So, different systems biology approach has

been used in various studies over diverse crop pathosystem to list out the key proteins involved in conferring resistance. Application of these advanced systems biology approaches in different crop against their target pathogen has been briefly illustrated in Table 1.

Table 1: List of some important pathogens studied by using different systems biology approach

Plant	Pathogen	Systems Biology approach used	Key findings	Reference
Wheat	<i>Rhizoctonia solani</i>	Transcriptomics	Found some novel microbial genes expressed in the rhizosphere of wheat roots upon infection of <i>R. solani</i>	Hayden <i>et al.</i> , (2018)
Rice	<i>Xanthomonas oryzae</i> pv. <i>oryzae</i>	Transcriptomics	Carried out the genome wide analysis of pathogenic gene expression profile of Rice- <i>X. oryzae</i> during the initial phase of interaction	Kim <i>et al.</i> , (2016)
Cassava	<i>Xanthomonas axonopodis</i> pv. <i>manihotis</i>	Transcriptomics	Identified full target repertoire of TAL14Xam668 in Cassava	Cohn <i>et al.</i> , (2016)
Arabidopsis	<i>Pseudomonas syringae</i>	Transcriptomics	Reported that jasmonate repressor JAZ5 and JAZ10 suppresses coronatine (COR) cytotoxicity and pathogen growth	de Torres Zabala <i>et al.</i> , (2016)
Wheat	<i>Fusarium graminearum</i>	Genomics	Identified virulence associated genes	Urban <i>et al.</i> , (2015)
Tobacco	Odontoglossum ringspot virus	Integrated omics (NGS, proteomics and transcriptomics)	Reported the host proteins interacting with the viral capsid protein	Lin <i>et al.</i> , (2015)
Tomato	<i>Fusarium oxysporum</i> f.sp. <i>radices-lycopersici</i>	Proteomics	Analyzed the impact of grafting combination of different scion-root stock on plant defense response	Vitale <i>et al.</i> , (2014)
Potato	Potato virus X	Transcriptomics	Carried out small RNA sequencing for differentiating various viral strains	Kutnjak <i>et al.</i> , (2014)
Sunflower	<i>Goloviromyces orontii</i>	Proteomics	Reported the key proteins those are accumulated in resistant genotypes of sunflower upon infection	Kallamadi <i>et al.</i> , (2018)
Sunflower	<i>Orobanche cumana</i>	Proteomics	Identified various proteins and pathways that are regulated under compatible and incompatible interaction	Yang <i>et al.</i> , (2017)
Chilli	<i>Fusarium oxysporum</i>	Proteomics	Investigated <i>F. oxysporum</i> defense related proteins in the chilli plant	Wongpia and Lomthaisong, (2010)
Soybean	<i>Xanthomonas axonopodis</i> pv. <i>glycines</i> (Xag)	Proteomics	Studied the <i>Bacillus amyloliquefaciens</i> KPS46 mediated systemic protection in soybean (<i>Glycine max</i> L.) against Xag	Buensanteai <i>et al.</i> , (2009)
Bean	<i>Uromyces appendiculatus</i>	Proteomics	Reported the basal and R-gene-mediated plant defenses	Lee <i>et al.</i> , (2009)
Mint	<i>Alternaria alternata</i>	Proteomics	Investigated the comparative proteomics of non-model unsequenced plants like <i>Mentha</i> upon infection with <i>A. alternata</i>	Sinha <i>et al.</i> , (2009)
Arabidopsis	<i>Plectosphaerella cucumerina</i> , <i>Fusarium oxysporum</i> and <i>Colletotrichum higginsianum</i>	Transcriptomics	Investigated the role of miR773 in modulating resistance to infection by fungal pathogens	Salvador-Guiraoet <i>et al.</i> , (2017)
Pea	<i>Orobanche crenata</i>	Proteomics	Identified differentially expressed proteins between two <i>O. crenata</i> infected pea genotypes differing in their Orobanche sensitivity	Castillejo <i>et al.</i> , (2004)
Citrus	Citrus tristeza virus	Transcriptomics	Reported the role of endogenous and exogenous RNA-derived sRNA species in the plant-defense response	Visser <i>et al.</i> , (2017)
Barrel medic	<i>Orobranche crenata</i>	Proteomics	Identified various proteins which show resistance against <i>O. crenata</i>	Castillejo <i>et al.</i> , (2009)
Rice	<i>Rhizoctonia solani</i>	Proteomics	Reported basal and R-gene-mediated plant defenses at the proteomic level.	Lee <i>et al.</i> , (2009)
Tomato	<i>Ralstonia solanacearum</i>	Proteomics	Reported 12 proteins which confer resistance	Dahal <i>et al.</i> , (2009)
Pear	<i>Erwinia amylovora</i>	Genomics	Found that the two-component signal transduction systems in <i>E. amylovora</i> played major roles in establishment of virulence	Zhao <i>et al.</i> , (2009)
Potato	<i>Phytophthora infestans</i>	Transcriptomics	Reported that Phenazine-1 carboxylic acid is involved in <i>P. infestans</i> growth repression and led to important transcriptomic changes	Roquigny <i>et al.</i> , (2018)
Wheat	<i>Zymoseptoria tritici</i>	Transcriptomics	Reported some resistant genes triggered in	Ma <i>et al.</i> , (2018)

			response to <i>Z. tritici</i> infection	
Wheat	<i>Puccinia triticina</i>	Transcriptomics	Identified Lr28 mediated genome-wide response upon infection with <i>P. triticina</i>	Singh <i>et al.</i> , (2017)
Tobacco	<i>Phytophthora palmivora</i>	Transcriptomics	Reported the <i>P. palmivora</i> pathogenomics and effector-aided resistance	Evangelisti <i>et al.</i> , (2017)
Soybean	<i>Rhizoctonia solani</i>	Transcriptomics and Metabolomics	Identified the candidate genes and metabolites involved in conferring resistance against <i>R. solani</i> infection	Copley <i>et al.</i> , (2017)
African rice	<i>Meloidogyne graminicola</i>	Transcriptomics	Identified novel set of candidate genes showing resistance against nematode	Petitot <i>et al.</i> , (2017)
Maize	<i>F. verticillioides</i>	Proteomics	Reported accumulation of specific pathogenesis-related proteins in tissues of the fungal-infected seeds	Campo <i>et al.</i> , (2004)
Wild tomato	<i>Clavibacter michiganensis sp. michiganensis</i>	Proteomics	Identified set of proteins conferring resistance against the bacteria	Coaker <i>et al.</i> , (2004)
Black gram	Mungbean Yellow Mosaic Virus	Proteomics	Studied molecular events occurring during compatible and incompatible interactions between plant and pathogen	Kundu <i>et al.</i> , (2011)

2.1 Comparative proteomics approach for fungal disease study

Fungal pathogens are responsible for causing a huge annual loss to crops, so it is very essential to understand the mode of infection of fungal diseases in order to figure out the candidate genes/proteins targeted by pathogens, the proteins involved in triggering the immune response and the virulence factors involved in causing the disease. Proteomics has emerged as one of the most reliable tool to tackle this problem and recently several works has been done in this field (Fernandez *et al.*, 2010; Afroz *et al.*, 2011; Doyle, 2011)^[33, 2, 24]. It is well known that one of the major threats to tomato cultivation is posed by the wilt disease caused by *Fusarium oxysporum f. sp lycopersici* (FOL), so in order to understand the mechanism of disease caused by FOL the total proteome of 20 isolates were analyzed, out of these 20 isolates two isolates FOL-8 and FOL-20 were characterized as virulent and least virulent strain respectively. Proteomic analysis has revealed that around 17 different proteins of which 3 proteins were downregulated and 14 proteins were significantly upregulated in FOL-8 in comparison to FOL-20. Mass spectrometric analysis of these differentially expressed proteins has shown that these proteins belong to different functional groups which were involved in pathogenicity and in establishing the infection on tomato root tissue. Overall, these experiments have unraveled some key proteins involved in the virulence of the pathogen in causing wilt disease (Manikandan *et al.*, 2018). *F. oxysporum* secrete several toxins during tomato wilt disease development amongst which fusaric acid is the most potent pathogenicity factor. So, in order to find out the role of fusaric acid in fungal pathogenicity the total proteome of the leaves was analyzed upon infiltration with fusaric acid. Several unique proteins were detected which were showing differential expression upon fusaric acid treatment. Hence, this study clearly shows that fusaric acid plays an important role in inducing the downstream signaling mechanisms which ultimately triggers fungal pathogenicity (Singh *et al.*, 2017)^[68]. Another research group has carried out the analysis of proteins known to be secreted by vascular wilt fungi to determine their role in pathogenicity and plant immunity. The whole-genome sequencing and proteomics screens have revealed the involvement of many proteins, including cysteine-rich proteins, necrosis-inducing proteins and many enzymes (de Sain and Rep, 2015). Recently, the proteome analysis of extracellular matrix (ECM) in vascular wilt resistant chickpea cultivar upon *F. oxysporum* infection has provided an insight

to the downstream mechanism involved in the cell wall mediated innate immunity response. Around 166 immune responsive proteins (IRPs) have been reported to be differentially expressed of which includes mostly amine oxidase, thioredoxin, nascent aminopolypeptide complex (NAC) and chaperonins. This detailed analysis has provided an idea about the complex signaling network operating in the ECM and the mechanism of innate immunity during disease in crop plant (Elagamey *et al.*, 2017)^[26].

Another devastating disease of tomato is the leaf mold disease caused by *Cladosporium fulvum*. It causes disease by producing extracellular small secreted proteins (SSP) effectors. Plants show resistance by means of their Cf immune receptor like proteins which recognize their specific SSPs to render the pathogen avirulent by triggering hypersensitive response (Wulff *et al.*, 2009)^[83]. The combined use of proteomics and transcriptomics approach has resulted into the finding of many novel Cf immune receptor like proteins (RLPs) and SSPs. Hence these novel Cf genes can be introduced in cultivated tomato for imparting resistance against *C. fulvum* (Mesarich *et al.*, 2017).

Rice blast is a major disease of rice which is caused by *Magnaporthe oryzae*. Phosphoproteomics based approach has been employed to analyze the phosphoregulation of *M. oryzae* during appressorium development. Transcriptomic, proteomic, and phosphoproteomic analysis has revealed some novel candidates involved in the regulation and metabolism during appressorium formation. Several transcription factors have been reported to be phosphoregulated during appressorium formation. Further functional analysis of the bHLH transcription factor MGG_05709 has provided some evidence for the role of protein phosphorylation in regulation of appressorium formation. These data have provided an insight into the role of protein phosphorylation during infection-related development (Franck *et al.*, 2015)^[32]. In *M. oryzae* deletion of a conidial gene encoding putative transcriptional regulator COM1 in *M. oryzae* resulted in aberrant conidial shape, reduced conidiation and attenuated virulence. Further analysis of the conidial proteomes of COM1 deletion mutant and its isogenic wild-type strain P131, has revealed several unique differentially expressed proteins. The data obtained from this study suggest that the COM1p plays a key role in transcriptional reprogramming of genes involved in melanin biosynthesis, carbon and energy metabolism, structural organization of cell, lipid metabolism, and amino acid metabolism (Bhadoria *et al.*, 2010)^[7].

Not only in *M. oryzae* but it has been reported in many other pathogens as well that phosphorylation plays an important role in downstream signaling during disease establishment. Hence, phosphoproteome of *Candida albicans*, have been analyzed and several unique phosphosites on proteins were identified. Phosphosites were also identified in protein like mediator, which was further confirmed through in vitro assays. This work has provided deep insights into the *C. albicans* phosphoproteome and specific phosphoproteins in disease establishment (Willger *et al.*, 2015) [79].

Oomycete *Phytophthora capsici* which is responsible for the losses of the vegetable production worldwide is one of the major threat which leads to a huge annual loss (Granke *et al.*, 2009) [35]. Hence different approaches were used to understand the mechanism of its infection. In accordance with this recently the proteomic analysis of the two asexual life stages of the *P. capsici* was carried out. It was found that the proteins upregulated in the mycelium are mainly associated with glycolysis pathway, citric acid cycle and the pentose phosphate pathway, which are involved in providing the needful energy for the hyphal growth. However, in case of cysts the proteins involved in fatty acid degradation were upregulated, this suggests that during the initial stage of infection the pathogen depends upon fatty acid degradation to meet its energy demand. This detailed proteomic analysis has provided some important information about the putative metabolic targets of the pathogens involved in establishing the plant-pathogen interaction in their two different developmental stages. Further, this information can be used in future studies to design suitable strategies to make resistant plant varieties that can cope up against the pathogen attack (Pang *et al.*, 2014) [59].

Like rice in wheat the total proteome of the resistant (cv. Shafir) and susceptible (cv. Obelisk) cultivars have been carried out upon inoculation with *Zymoseptoria tritici* strain IPO323. The reports suggest that several fungal proteins which include the cell-wall degrading enzymes and proteases, might play a role in pathogenicity, but the functions of many of these proteins were still remain unknown. This work has provided some information about the specific role of these proteins in establishing the pathogenesis in wheat (M³Barek *et al.*, 2015) [49].

2.1.2 Proteomics approach for studying plant defense system

Systemic acquired resistance (SAR) provides a broad-spectrum resistance in plants, proteomic analysis of the phloem exudates in *Arabidopsis* in response to the induction of SAR upon *Pseudomonas syringae* infection has revealed that around 16 unique proteins were upregulated and 46 proteins were downregulated in phloem exudates. Most of these proteins were reported to contribute to the SAR response. In this way these studies have helped to find out the downstream mechanisms underlying in SAR (Carella *et al.*, 2016) [13]. Another group has used two near-isogenic cultivars with different levels of disease resistance. They analyzed the total proteome of these two cultivars after methyl-jasmonate (MeJA) treatment, phenotypic analysis revealed that both the cultivars increased resistance against *M. oryzae* upon MeJA treatment. But the treated resistant cultivar maintained a higher level of resistance in comparison to the same treated susceptible cultivars. Total proteome analysis revealed that many unique MeJA-influenced proteins were induced upon MeJA treatment. Their data has provided an idea about the

mechanisms of overall MeJA-induced defense response in rice (Li *et al.*, 2014).

It has been reported previously that NO plays an important role in plant defense response, so in order to get a deeper insight into the role of NO mediated plant defense response the total proteome of *Arabidopsis* wild type (WT) and GSNO-reductase mutant plants was carried out upon infection with both the avirulent and virulent pathogen strains of *P. syringae*. It was found that both WT and mutant plants have shown strong resistance to avirulent strains upon infections in comparison to the virulent strains. The total proteome analysis has shown that this resistance was observed mainly due to the upregulation of stress, redox and those involved in triggering the defense response. Further, upon infection with virulent strains, the majority of proteins which were found to be upregulated were those which trigger the defense response, but there was very little upregulation of redox and stress response proteins (Holzmeister *et al.*, 2011) [38].

It is well known that the PM H⁺-ATPases are dynamically regulated during plant immune responses. The PM H⁺-ATPases has been reported earlier to interact with the plant immune signaling protein RIN4 which in turn regulate stomatal apertures during bacterial invasion of leaf tissue. But pathogens have evolved several mechanisms to manipulate PM H⁺-ATPase this interaction which is important to initiate the process of infection. In this way the PM H⁺-ATPase plays an important role in the plant immune responses, which was targeted by many pathogens which makes the plant susceptible against the respective pathogens. Hence proteomic analysis has been carried out to find the roles of the plasma membrane (PM) H⁺-ATPase during plant-pathogen interactions (Elmore & Coaker, 2011) [27].

2.2 Proteomics role in bacterial disease study

Bacterial diseases are widespread across the globe and they infect a wide range of agriculturally important crops. In order to control these diseases different strategies have been designed that range from plant breeding to genetic engineering approaches. Although by employing genetic engineering as a tool, it is possible to introgress a resistant gene not only from different genus but even from prokaryotic species as well for making resistant varieties which is generally not possible through conventional breeding methods. But, to achieve this it is essential to have a profound knowledge about the virulence, mode of infection, protein targets and downstream signaling pathways of the different agriculturally important bacterial pathogens. Proteomics a systems biology approach can here play an important role to generate huge amount of information in order to understand the complex biology of plant-pathogen interaction. In past decade many works have been done in this field but still there is a huge void in our knowledge about many important bacterial pathogens and hence further research work is needed to be carried out for deciphering the complex mechanism of disease establishment about all important plant-pathogens.

In the last decade huge amount of work has been done on some deadly bacterial plant pathogens that cause a huge loss to some agriculturally important crops across the globe. Among these the genus *Xanthomonas* constitutes the most devastating group which causes severe crop losses. In order to control this pathogen, it is essential to have a detailed knowledge about its mode of infection. For this purpose, the bacterium was infiltrated into leaves of the susceptible cultivar followed by total proteome analysis. This approach in turn has provided some valuable information about the novel

proteins involved in establishing the infection, which is useful to design ways to overcome its infection (Andrade *et al.*, 2008) [5].

The comparative proteomics and bioinformatics approach has been used to determine the downstream virulence mechanism of *Xanthomonas oryzae* infection in rice plants. For this purpose, the strain PXO99A has been used and around 15 Tat-dependent translocation proteins (TDTP) were reported to be involved in the Tat pathway of *X. oryzae* pv. *oryzae* mediated infection (Wu *et al.*, 2017) [82].

Further it has been reported that the *Xanthomonas* genus mainly depends upon the type III secretion system and several other factors for their pathogenicity, till date many species of the genera have been sequenced. So, by comparing the genomic and proteomics data together it is possible to generate a wide range of information. Hence, by using the proteogenomic approach several unique protein coding genes can be identified which in turn provide deeper insight about the Xanthomonadaceae genomes, providing better understanding for future studies (Abendroth *et al.*, 2017) [1].

The bacteria *Erwinia amylovora* causes the fire blight disease in apple and pear which results in a huge annual loss (Pulawska *et al.*, 2012; EPPO, 2013) [29]. Hence, in order to study its mode of infection and to get a detailed insight into the proteins involved in virulence response the total proteome was analyzed upon inoculation with highly virulent *E. amylovora* strain. Comparison of total proteome was carried out between a highly virulent and a less virulent strain. Comparison of the two bacterial isolates has revealed that the proteins involved in virulence, sorbitol metabolism and amylovoran production were highly upregulated in the highly virulent strain. This study has provided a detailed insight about the mode of infection *E. amylovora* which is essential for the researchers in near future to develop resistant variety that can cope up better against the *E. amylovora* infection (Holtappels *et al.*, 2016) [36]. They further analyzed the two strains of *E. amylovora* and found that two proteins FliC and CheY which were essential for maintaining the flagella structure, motility and chemotaxis were abundant in the least virulent strain whereas the GalF protein which is involved in amylovoran production was significantly upregulated in the highly virulent strain. These results revealed that not only the bacterial proteins but the flagellin proteins also play an indirect role in eliciting plant defense mechanism (Holtappels *et al.*, 2015) [37]. One interesting study has shown that not only plant pathogens but some human pathogens can even move inside the food crops *via* roots and through surface uptake. A quantitative proteomics approach was used to find out change in the pattern of protein expression in lettuce upon internalization of *Salmonella* enteric *Serovar infantis*. Total protein was analyzed from lettuce leaves upon infiltration of *S. infantis*, results revealed that the glycolysis related proteins were down-regulated, while those involved in ascorbate uptake was up-regulated. Stress response proteins, especially antioxidant proteins, were up-regulated. This change in the expression pattern shows that even the human pathogen can trigger the defense response mechanism in lettuce which generally occurs in response to plant pathogens only (Zhang *et al.*, 2014) [47].

2.2.1 Systems biology approach to study plant defense response upon bacterial attack

It is a well-known fact that plants respond immediately to the pathogen attack and among which systemic acquired resistance (SAR) is the major innate immunity system which

functions in response to a pathogen attack (Van Loon *et al.*, 1998) [73]. In rice, proteomics approach was used to study the SAR response upon bacterial infection. For this study rice cv. Java14 seedlings were used which were inoculated with a compatible (Xo7435) and incompatible (T7174) strain of *X. oryzae* pv. *oryzae* (Xoo). Further, the proteins were isolated after treatment and were used for the total proteome analysis. Among the total 366 proteins analyzed 20 were reported to be differentially expressed upon bacterial inoculation which was categorized into different functional group. Out of these 20 proteins 5 proteins have shown a significant change in the level of accumulation upon Jasmonic acid (JA) treatment. This is in accordance with the previous reports which suggest that JA plays an important role in imparting resistance in plants upon pathogen attack (Van Peer *et al.*, 1991; Dong, 1996). Mass spectrometric analysis has revealed that the thaumatin-like protein and probenazole-inducible protein (PBZ) were highly upregulated both upon bacterial inoculation and JA treatment. Altogether, this study has given a detailed idea about the defense response pathway of plants upon bacterial infection (Mahmood *et al.*, 2006) [50].

2.2.2 Integrated omics approach to develop potential biocontrol or antimicrobial agent

Apart from these pathogens mentioned above there are several other pathogens which are badly affecting the vegetable production. Among these a necrotrophic group of bacteria is gaining the major concern as they are causing huge loss to potato cultivation in the European countries. This group of necrotrophic bacteria includes mainly *Pectobacterium* spp. and *Dickeya* spp. It has been reported that there are some lytic bacteriophage strains *viz.* *Pectobacterium carotovorum* subsp. *carotovorum* (Pcc), *P. wasabiae* (Pwa) and *Dickeya solani* (Dso) that have the capability to attack these necrotrophic bacteria's and serve as a strong biocontrol agent for future use. Hence, in order to gain a deeper knowledge about the phages ΦPD10.3 and ΦPD23.1 comparative genome sequencing and proteomics approach was used to understand its mechanism of action against this deadly pathogen (Czajkowski *et al.*, 2015) [19].

Recently, it has been reported that even food items can act as a potential antimicrobial agent. Iberin an isothiocyanate is one such compound which has been isolated from horseradish and generally acts as a quorum sensing inhibitor (QSI) in *Pseudomonas aeruginosa* (Truchado *et al.*, 2015) [72]. An integrated systems biology approach was used to understand its mode of action. Transcriptome analysis revealed that the iberin inhibits the expression of the GacA-dependent small regulatory RNAs RsmY and RsmZ. Further, proteomics analysis shows that iberin reduces the abundance of the LadS protein, an activator of GacS. Altogether these findings have provided detailed information about the mechanism of action of iberin on *P. aeruginosa* which in turn can be used in future for controlling this pathogen (Tan *et al.*, 2014) [71].

2.3 Proteomics role in viral disease study

Similarly, like bacteria and fungi, viruses are also known to cause deadly diseases in plants and there are a huge range of viruses known to infect crops. Hence, it is essential to design suitable strategies against these viral diseases as well and once again proteomics approach in combination with several other fields serves as a reliable tool to conquer this problem. Here, we have compiled some studies done in the last decade in the field of virology for studying the mode of infection of various important plant viruses through proteomics approach.

Viruses generally spread systemically and hence it is important to have a better understanding of the mode of systemic response. In order to get a deeper insight of systemic response quantitative proteomics was utilized. For proteomic analysis virus free leaves were used after few days upon local inoculation with oilseed rape mosaic virus. During this period the virus spread systemically inside the plant and triggered the systemic response. Results revealed that several stress related proteins were differentially regulated during systemic response. Among these the proteins involved in jasmonic and abscisic acid signaling, protein folding and synthesis, and carbohydrate metabolism were upregulated. Further, it was reported that the virus even triggers the inhibition of antiviral host defense mechanism which in turn is required for the spread of viral infection. Altogether these data give a better understanding of systemic response upon viral infection which can be used as a solid base for further studies in order to make some useful strategies for overcoming the viral infection (Niehl *et al.*, 2013)^[57].

In India tomato is one of the important vegetable crops and it is infected mainly by tomato blistering mosaic virus (ToBMV), the damage done by this virus is not limited to tomato crops only but it is known to infect several other dicotyledonous plants as well (Melo *et al.*, 2014; Ferrand *et al.*, 2015; Blawid, *et al.*, 2016)^[53, 31, 8]. These viruses replicate in the vesicles formed inside the chloroplasts. A detailed proteomic analysis has been carried out to find the mode of host pathogen interaction. Proteomic analysis of the ToBMV infected *Nicotiana benthamiana* has shown several differentially expressed proteins which belong mostly to the photosynthesis and defense related proteins. Further, several putative targets of plant-viral interaction have been reported which includes the ATP synthase β subunit, RNA polymerase beta-subunit, 50S ribosomal protein L6 and Trigger factor-like protein. Hence, this study has given a detailed idea about the various putative targets that may be involved in the plant-viral interaction and the mode of viral infection (Megias *et al.*, 2018)^[52].

Another such important pathogen is the cucumber mosaic virus which affects a wide range of agriculturally important crops (Mohamad Roff and Anang, 1989; Sidek and Sako, 1996). Till now no natural resistance genes have been reported against this virus hence several genetic engineering strategies were employed to generate resistant cultivars. One such strategy was to express a single-chain variable fragment antibody (scFv G4) in the plant. Expression of this antibody in tomato plant has shown considerable resistance against this viral infection. But in order to get a better insight into the antibody mediated resistance a comparative proteomic analysis between a susceptible cultivar and an immunoprotected tomato plant was carried out. Results revealed that several proteins were differentially regulated and among which majority of them were related to photosynthesis related proteins or defense response proteins. Altogether this study has revealed the mechanism of antibody mediated defense in plants (Di Carli *et al.*, 2015)^[22].

It has been reported that the Odontoglossum ringspot virus (ORSV) spreads systemically in *N. benthamiana* and for this movement, glutamic acid at position 100 (E100) is important. The ORSV (E100A) mutant shows a defect in systemic infectivity, it was found that E100 is important for capsid protein interaction and for the viral assembly. In order to get detailed information about the ORSV mode of infection an integrated omics approach was used. By using this approach several unique proteins were identified that were reported to

be interacting with ORSV capsid protein. It was found that majority of these proteins were either defense related proteins, cell division related proteins or the components of photosystem. Among these capsid interacting proteins a proteinase inhibitor of *N. benthamiana* (NbPI2) was found to be strongly associated with the capsid mutant CP (E100A) in comparison to the wild type capsid protein. However further research is needed to find out the role of NbPI2 in plant immunity. Altogether this study has provided some valuable information about the capsid interacting proteins which is required for the spread of systemic infection in plants (Lin *et al.*, 2015).

In India sugarcane is mainly used by the sugar industries although its production is affected by several pathogens but amongst all of them sugarcane mosaic virus (SCMV) is the major pathological agent which accounts for a huge annual loss to the total production. In order to get a detailed understanding of the key proteins involved in establishing the plant-virus interaction comparative proteomics approach was used and for this the total proteome of the resistant and susceptible cultivar were analyzed upon inoculation with the virus. Data revealed that a huge set of functional proteins were differentially regulated upon viral infection, majority of these proteins belongs to the energy and metabolism, stress and defense responses, photosynthesis, and carbon fixation (Wu *et al.*, 2015)^[82]. Proteins are known to be regulated post translationally also and among which phosphorylation is the most important factor. So not only comparative proteomics but phosphoproteomics approach is also essential to get a deeper insight into the mode of infection by SCMV. Analysis of susceptible and resistant cultivar upon infection has shown that phosphorylation of several unique proteins has significantly increased upon viral-infection. Among these phosphoproteins most of them were found to be involved in the defense response triggered by the plants Altogether, these studies have provided some information about the target proteins involved during the viral infection. Hence, this information can be used in future to develop suitable strategies to conquer this disease (Wu *et al.*, 2013)^[82].

Another deadly virus is Mungbean Yellow Mosaic India Virus (MYMIV) which severely affects the productivity of black gram (Verma *et al.*, 1992). Hence, in order to get some information about its mode of action proteomics approach was used in combination with the biochemical analysis. For the experimental analysis a susceptible and a resistant variety was used to understand the mechanism of plant virus interaction. The biochemical and proteomic data shows that in response to infection host plant shows significant accumulation of phenolics, hydrogen peroxide and upregulation of several other stress and defense response related proteins. Among the various defense response pathways, it was found that ascorbate peroxidase, rubisco activase and serine/glycine hydroxymethyl transferases are the major networks which were highly induced. Altogether this study has given detailed information about the key networks involved in triggering defense response upon viral infection (Kundu *et al.*, 2013)^[44].

In wheat it has been found that the virus induced gene silencing of a basic transcription factor 3 (BTF3) results into severe growth defects. This transcription factor is essential for the initiation of the RNA polymerase II and silencing of this gene in turn resulted into stunted growth, reduced height and total fresh and dry weights. In order to find out the key proteins involved in this mechanism proteomic approach was used. For the comparative proteome analysis the differentially

expressed proteins between the TaBTF3 virus-induced gene silenced wheat plants and the barley stripe mosaic virus-induced gene silencing green fluorescent protein transgenic wheat plants (control) were analysed. Several unique proteins have been identified in this study and which were found to be involved in signal transduction, stress defense, photosynthesis, carbohydrate metabolism, and protein metabolism (Kang *et al.*, 2013) [40].

PR proteins are also known to play an important role in triggering plants defense response upon infection (Van Loon, 1997; Neuhaus, 1999) [74]. It has been reported that the L(3) gene confers resistance against the tobamoviruses. Hence, a proteomic approach was used to study the PR proteins induced in *Capsicum chinense* PI159236 plants harbouring the L(3) gene in response to infection by the tobamovirus strains PMMoV-S or PMMoV-I. It was found that upon infection with these strains PMMoV-S a hypersensitive response was induced in these plants which leads to the inhibition of viral infection. Several PR proteins have been found to be induced in the host in response to the infection. Further it was reported that three PR proteins were significantly upregulated upon infection these are an acidic beta-1,3-glucanase isoform (PR-2), an osmotin-like protein (PR-5), and a basic PR-1 protein isoform (Elvira *et al.*, 2008). In crops, aphids are considered as one of the most devastating agents that act as a vector for many viral diseases (Brunt *et al.*, 1996; Nault, 1997; Eastop, 1983; Hull, 2002). Aphids directly inject their effector proteins into the host plants which in turn help them in phloem sap uptake. Hence, gaining a detailed knowledge about the evolution of aphid effectors may help to find a possible way to overcome its attack. In legumes comparative transcriptomics and proteomics approaches has been utilized to find out the candidate effectors genes from the Aphid *Acyrtosiphon pisum*. It has been reported that during the host-pathogen interaction a number of factors plays crucial role in establishing either defense response or suppressing the host defenses. Pathogens suppress the host defense system by various means out of which one is the use of effector proteins. Studies have shown that in the aphid *A. pisum* several genes were upregulated in the salivary glands in comparison to the alimentary tract. This study has given a clue about the large group of effector molecules of *A. pisum* that are involved in establishing its virulence response. (Boulain *et al.*, 2018) [9].

Conclusion

In the recent time systems biology has flourished as the most advanced field which can be used to solve the mysteries of complex biological systems. Integration of various highly advanced systems biology approaches has revolutionized the research in the field of plant pathology as they are capable of generating huge amount of information within a short span of time. With the development of these new technologies now it has become much easier to understand the molecular mechanism underlying during the plant pathogen interaction. Earlier, with the traditional methods it was impossible to have such a deeper insight into the mechanism of pathogenicity but with these modern scientific approaches now it's possible to look deep even into the molecular signaling occurring during plant-pathogen interaction. Although it's a challenging task and demands extensive research work to be carried out, but it has to be done anyhow because the global population is increasing at a tremendous rate and by 2050 it will become very difficult to feed the entire population. So, it is essential to design certain effective measures as soon as possible which

in turn will help to increase the annual productivity of agriculturally important crops.

Conflict of interest

The authors declare that they have no conflict issues while publishing the article.

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