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Plant Innate Immune Response: Qualitative and Quantitative Resistance

Ajjamada C. Kushalappa, Kalenahalli N. Yogendra, and Shailesh Karre

Plant Science Department, McGill University, Ste. Anne de Bellevue, Québec, Canada

ABSTRACT

Plant diseases, caused by microbes, threaten world food, feed, and bioproduct security. Plant resistance has not been effectively deployed to improve resistance in plants for lack of understanding of biochemical mechanisms and genetic bedrock of resistance. With the advent of genome sequencing, the forward and reverse genetic approaches have enabled deciphering the riddle of resistance. Invading pathogens produce elicitors and effectors that are recognized by the host membrane-localized receptors, which in turn induce a cascade of downstream regulatory and resistance metabolite and protein biosynthetic genes (R) to produce resistance metabolites and proteins, which reduce pathogen advancement through their antimicrobial and cell wall enforcement properties. The resistance in plants to pathogen attack is expressed as reduced susceptibility, ranging from high susceptibility to hypersensitive response, the shades of gray. The hypersensitive response or cell death is considered as qualitative resistance, while the remainder of the reduced susceptibility is considered as quantitative resistance. The resistance is due to additive effects of several resistance metabolites and proteins, which are produced through a network of several hierarchies of plant R genes. Plants recognize the pathogen elicitors or receptors and then induce downstream genes to eventually produce resistance metabolites and proteins that suppress the pathogen advancement in plant. These resistance genes (R), against qualitative and quantitative resistance, can be identified in germplasm collections and replaced in commercial cultivars, if nonfunctional, based on genome editing to improve plant resistance.

I. Introduction

Plant pathogens are of huge economic importance as they threaten our food, fiber, and bioproduct production under field conditions and further in storage. Genetic improvement of plants is the best way to manage these losses. Molecular biologists have identified hundreds of disease resistance quantitative trait loci (QTLs), in several plant-pathogen systems, but their use in breeding is challenging because they contain several genes, including undesirable ones (Aghnoum *et al.*, 2010; Ashkani *et al.*, 2014; Buerstmayr *et al.*, 2009; St. Clair, 2010). With the advent of sequencing of several plant and pathogen genomes, novel technologies have evolved including metabolomics, proteomics, and transcriptomics in addition to genomics and epigenomics (OMICs), offering new opportunities to unravel the mechanisms of qualitative and quantitative resistance in plants (Kushalappa and Gunnaiah, 2013; Liu *et al.*, 2013b). In this review, we focus on hierarchies of regulatory and resistance metabolite and protein biosynthetic genes induced in plants following pathogen perception, in addition to those constitutively present, to produce resistance metabolites and proteins that directly suppress pathogen development in plants, leading to reduced susceptibility. Also, their deployment in improving crop plant resistance against microbial stress is based on genome editing tools.

II. Plant-pathogen interaction

Plants, unlike mammals, lack adaptive immunity but they have innate immune system in each cell with systemic signaling capability from infection sites (Jones and Dangl, 2006). Pathogens produce elicitors called pathogen/microbe-associated molecular patterns (PAMP/MAMP), including peptides, metabolites, cell wall components, enzymes, and toxins to suppress plant defense (Boller and

Felix, 2009; Dodds and Rathjen, 2010; Giraldo and Valent, 2013; Wirthmueller *et al.*, 2013). Following pathogen attack, the damaged host produces damage-associated molecular patterns (DAMP), including plant signal molecules (Boller and Felix, 2009). These elicitors or PAMP/MAMP/DAMP are recognized by the pattern recognition receptors (PRRs) that are biosynthesized in endoplasmic reticulum and transported to plasma membrane (Frescatada-Rosa *et al.*, 2015). As a first line of defense response, the PAMP/MAMP trigger downstream genes resulting in no symptoms or race-non-specific hypersensitive response, generally referred to as the PAMP/pattern-triggered immunity (PTI) or non-host resistance (Baxter *et al.*, 2014; Boller and Felix, 2009; Dodds and Rathjen, 2010; Macho and Zipfel, 2015; Stael *et al.*, 2015; Trdá *et al.*, 2015; Uma *et al.*, 2011). The genotypes rendered susceptible are considered to vary in basal resistance, partial resistance, or horizontal resistance (Jones and Dangl, 2006; Niks *et al.* 2015; Dodds and Rathjen, 2010).

Specialized pathogens produce race-specific intracellular elicitors called effectors, produced by specific avirulence (AVR) genes (Boller and Felix, 2009; Oliver and Solomon, 2010). Though these are considered to be specific to biotrophs, several necrotrophs also produce effectors (Boller and Felix, 2009). These effectors suppress other PAMPs and also the host resistance genes to become more virulent (Lo Presti *et al.*, 2015). The effectors, depending on their domains, are recognized by plant-produced specific receptors (R proteins), encoded by *R* genes (Boller and Felix, 2009; Du *et al.*, 2015; Jones and Dangl, 2006; Sarris *et al.*, 2015). As a second line of defense response, the effectors trigger downstream genes resulting in race-specific hypersensitive response to contain the pathogen, generally referred to as the effector-triggered immunity (ETI), qualitative resistance, or vertical resistance (Boller and Felix, 2009; Giraldo and Valent, 2013). Such a resistance is considered to be monogenic and spawned the gene-for-gene hypothesis (Flor, 1971). However, these effector recognition receptor genes are just surveillance genes and the real resistance genes that induce hypersensitive response are NADPH oxidase, callose synthase, etc., genes, which are reviewed in the next section. The genotypes rendered susceptible are considered to vary in basal resistance, partial resistance, or horizontal resistance (Dangl and Jones, 2001; Niks *et al.* 2015; Dodds and Rathjen, 2010).

The hallmark of ETI is the hypersensitive response or cell death, where the pathogen advancement in plant is completely suppressed by the effector-triggered downstream genes, following a complete suppression of PTI by effectors. Similarly, in PTI, the pathogen advancement is completely suppressed by the PAMP/pattern-triggered downstream genes, without any symptom or with hypersensitive response, following the absence of PTI suppression by effectors, also called non-host resistance (Dodds and Rathjen, 2010; Jones and Dangl, 2006). An incomplete suppression of PTI by effectors enables pathogen to advance, leading to basal or quantitative resistance (Niks *et al.*, 2015). In this review, we consider both ETI and PTI to be qualitative resistance, where the plant immune response is either a complete resistance with hypersensitive response or susceptibility. Whereas a weaker immune response, PTI and ETI response, with a lack of hypersensitive response, due to reduced or non-functionality of genes that produce effectors/R proteins, and PAMP/PRR proteins, and also due to the production of enzymes and toxins by pathogens, enabling the pathogen to advance further is considered incomplete resistance, partial resistance, basal resistance or quantitative resistance, the third line of defense (Boyd *et al.*, 2013; Kim and Hwang, 2015; Niks *et al.*, 2015; Uma *et al.*, 2011; Waszczak *et al.*, 2015). All the same, neither the distinction between qualitative and quantitative resistance nor between the PTI and ETI is always clear, rather they are shades of gray (Poland *et al.*, 2009).

A. *Setting up the stage: Unifying concept of resistance and the terminologies*

Here we propose a unifying concept of resistance. The resistance in plants to pathogen attack is expressed as reduced susceptibility, ranging from complete susceptibility to hypersensitive response, the shades of gray. The hypersensitive response or cell death is considered as qualitative resistance, while the remainder of the reduced susceptibility is considered as quantitative resistance. The quantitative resistance can be quantified either based on monocyclic process under greenhouse conditions as infection efficiency, latent period, lesion expansion, and amount of sporulation or as polycyclic process under field conditions as apparent infection rate and area under the disease progress curve (Kushalappa and Gunnaiah, 2013). The resistance in plants against pathogen stress is controlled by a hierarchy of genes, designated here as *R* genes with subscripts based on their functions, which eventually produce resistance-related (RR) metabolites (RRMs) and proteins (RRPs) that directly suppress the pathogen based on their antimicrobial properties or enforce cell walls to contain them. Following invasion, the pathogens produce elicitors (former: PAMP/MAMP) which are recognized by the plant elicitor recognition receptors (ELRRs produced by R_{ELRR} genes; former: PRR), and the specialized pathogens produce more virulent elicitors called effectors that are recognized by the effector recognition receptors (ERR by R_{ERR} genes; former: receptor proteins by R genes). In turn, they induce

a hierarchy of downstream genes such as phytohormones (PHR by R_{PHR} genes), mitogen-activated protein kinases (MAPKs by R_{MAPK} genes), and transcription factors (TFs by R_{TF} genes), which regulate downstream genes that biosynthesize RRMs (by R_{RRM} genes) and RRPs (by R_{RRP} genes) (Table 1) (Kushalappa and Gunnaiah 2013). Following recognition of elicitors the R_{ELRR} genes induce elicitor-triggered immunity (ELTI; former: PTI), whereas following recognition of effectors the R_{ERR} genes induce ETI (former: same), both produce hypersensitive response, thus considered qualitative resistance. A weaker or absence of ELTI or ETI, due to non-functionality of genes involved and also due to their suppression by other elicitors, such as enzymes and toxins, enable the pathogen to advance, but are then suppressed by RRMs and RRPs leading to reduced susceptibility or quantitative resistance. The hypersensitive response, however, is also controlled by several genes that produce different resistance metabolites (RRM; callose) and proteins (RRP; chitinases), and so is the quantitative resistance. The amount of resistance thus depends on the type and abundances of RRM and RRP produced, which in turn depends on the hierarchy of genes that regulate them; rather the resistance is a product of the network of a hierarchy(ies) of R genes (Figure 1; Table 1) (Boyd et al., 2013; Brosché et al., 2014; Kushalappa and Gunnaiah, 2013; Liu et al., 2013a; Yogendra et al., 2015a). The products of a network of hierarchies of R genes (italicized R with subscripts representing their functions) involved can be represented by a simplified model:

$$\text{Resistance} = \sum_{n}^{i=1} (R_{ELRR} \text{ or } R_{ERR} {}^*R_{PHR} {}^*R_{MAPK} {}^*R_{TF} {}^*R_{RRM} \text{ and/or } R_{RRP}),$$

where i is the ith hierarchy and n is the total number of hierarchies in a given genotype. The quantitative resistance is mainly due to additive effects of several such hierarchies of R genes that produce several RRMs and RRPs, which can be constitutive RR metabolites or proteins (RRC) or induced following pathogen invasion, the induced RR metabolites and proteins (RRI), suppressing pathogen by antimicrobial properties of RRM and RRP or further enforcement of cell walls by producing structural barriers (Kushalappa and Gunnaiah, 2013). Thus, a RRM or RRP is produced by a hierarchy of R genes, which are rather a chain of genes, and a missing link with a nonfunctional R gene would lead to reduced abundance or absence of a given RRM or RRP, resulting in reduced or no resistance contribution from that hierarchy. The R genes in a hierarchy, however, may have complex interactions with each other; for example, a TF can regulate several RRM genes and likewise a RRM gene can be regulated by several TF genes, thus affecting the abundances of several RRMs. These R genes, however, may have either functional (R) or nonfunctional (r) alleles. These R genes are often associated with several single nucleotide polymorphisms (SNPs) but all SNPs do not have similar values for the quality of protein produced, some may have minor effects on protein expression, while others with SNPs in domain regions may have detrimental effect on protein or enzyme quality. The R genes may control either a major or a minor trait or phenotype. More comprehensive studies, based on systems biology, are needed to unravel several interactions among the R genes in a hierarchy and also the interactions among hierarchies of R genes, involved in plant innate immune responses, the qualitative and quantitative resistance.

III. Hierarchies of Genes (R) Involved in Resistance

The resistance in plants against pathogen stress is mainly due to RRP and RRM, which are present only in, or in higher amounts, in resistant than in the susceptible genotype. These RRP and RRM are produced either constitutively (RRC) or induced (RRI) following pathogen invasion. The resistance is due to their antimicrobial properties or they are deposited to enforce cell walls, forming structural components, thus containing the pathogen (Kushalappa and Gunnaiah, 2013). These RRM and RRP are produced by R genes, which are regulated by a network of a hierarchy of R genes: receptors (ELRR/ERR), phytohormones (PHR), MAPKs (MAPK), and TFs (TF) genes, and they biosynthesize RRM and RRP that suppress pathogen advancement in plant leading to reduced susceptibility, including hypersensitive response. Any of these R genes can be replaced in a commercial cultivar, if its allele is nonfunctional (r gene), based on genome editing, to improve resistance against pathogen stress.

A. Plant receptor (ELRR and ERR) genes and regulation of downstream genes

The plant receptors localized at plasma membrane are receptor-like kinases (RLKs), which at C-terminal end bind to elicitors at the apoplast, and at N-terminal bind to kinases in the cytosol, or receptor-like proteins (RLPs), which have no intracellular kinase domains (Macho and Zipfel, 2015). The AVR genes produce hundreds of race-specific effectors that are recognized by specific receptors (ERR), belonging to the coiled-coil, nucleotide-binding, leucine-rich repeat (CC-NB-

Table 1. Resistance genes (*R*), including regulatory (*ELLR, ERR, PHR, MAPK, TF*) and resistance-related metabolite (*RRM*) and resistance-related protein (*RRP*) biosynthetic genes (*R*), induced in plants against biotic stress resistance.

A. Regulatory genes (*R*) imparting biotic stress resistance in plants				
Gene name	Role	Crop	Pathogen	Reference
ELICITOR AND EFFECTOR RECOGNITION RECEPTOR GENES (*ELRR* and *ERR*)				
R1 (receptor gene)	Receptor activity	Potato	*Phytophthora infestans*	(Yogendra *et al.*, 2015b; Yogendra *et al.*, 2014)
ELR (receptor-like protein)	Elicitin recognition	Potato	*Phytophthora infestans*	(Bellés *et al.*, 2008)
Xa39	Broad-spectrum hypersensitive response R gene	Rice	*Xanthomonas oryzae pv. oryzae*	(Zhang *et al.*, 2015)
LecRK-VI.2	Activates pattern-triggered immunity	Arabidopsis	*Pseudomonas syringae pv. tomato*	(Yeh *et al.*, 2015)
FLAGELLIN-SENSITIVE 2 (FLS2) receptor kinase	Initiates downstream defense response	Arabidopsis	*Pseudomonas syringae pv tomato*	(Zeng and He, 2010)
CERK1	Crucial for chitin elicitor signaling	Arabidopsis	*Alternaria brassicicola*	(Miya *et al.*, 2007)
ZmWAK	Confers quantitative resistance	Maize	*Sporisorium reilianum*	(Zuo *et al.*, 2015)
LysM RLK1	Essential for chitin signaling	Arabidopsis	*Erysiphe cichoracearum*	(Wan *et al.*, 2008)
TaCPK2-A	Activate immune and stress signaling networks	Rice	*Blumeria graminis tritici*	(Geng *et al.*, 2013)
NbWIPK and NbSIPK	Activates downstream defense signaling against pathogen-derived elicitors	*Nicotiana benthamiana*	*Pseudomonas cichorii, Phytophthora infestans*	(Sharma *et al.*, 2003)
MITOGEN-ACTIVATED PROTEIN KINASES (*MAPKs*)				
CML9	Regulates flagellin-dependent signaling pathway	Arabidopsis	*Pseudomonas syringae*	(Leba *et al.*, 2012)
SlMKK2 and SlMKK4	Positive regulator of defense response	Tomato	*Botrytis cinerea*	(Li *et al.*, 2014)
GhMPK16	Activation of multiple signal transduction pathways	Arabidopsis	*Colletotrichum nicotianae, Alternaria alternate, Pseudomonas solanacearum*	(Shi *et al.*, 2011)
OXI1 protein kinase	Regulates effector-triggered immunity	Arabidopsis	*Hyaloperonospora parasitica, Pseudomonas syringae*	(Petersen *et al.*, 2009)
OsNPR1/NH1	Regulator of SA-mediated resistance	Rice	*Xanthomonas oryzae pv. oryzae*	(Gallego−Giraldo *et al.*, 2011)
TRANSCRIPTION FACTOR GENES (*TF*)				
OsWRKY13	Activator and suppressor of SA and JA pathways, respectively	Rice	*Xanthomonas oryzae pv. Oryzae Magnaporthe grisea*	(Giberti *et al.*, 2012)
GhWRKY44	Positive regulation of plant-pathogen interaction	*Nicotiana benthamiana*	*Ralstonia solanacearum, Rhizoctonia solani*	(Li *et al.*, 2015a)
GaWRKY1	Regulates biosynthesis of sesquiterpene phytoalexins	Cotton	*Verticillium dahliae* extracts	(Xu *et al.*, 2004)
OsWRKY89	Regulation of wax and lignin biosynthesis	Rice	*Magnaporthe oryzae*	(Wang *et al.*, 2007)
OsWRKY30	Positively regulates PR10 defense gene	Rice and Arabidopsis	*Pectobacterium carotovora, Xanthomonas campestris, Xanthomonas oryzae*	(Lee *et al.*, 2013)
WRKY8	Regulates abscisic acid and ethylene signaling pathways	Arabidopsis	Tobacco mosaic virus	(Chen *et al.*, 2013)
SlDRW1	Positive regulator of defense response	Tomato	*Botrytis cinerea*	(Liu *et al.*, 2014a)
TaPIMP1	Regulation of Abscisic acid (ABA) and SA signaling pathway genes	Wheat	*Bipolaris sorokiniana*	(Zhang *et al.*, 2012)
SlSRN1	Positive regulator of defense response	Tomato	*Botrytis cinerea, Pseudomonas syringae pv. tomato*	(Liu *et al.*, 2014b)

(*Continued*)

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A. Regulatory genes (*R*) imparting biotic stress resistance in plants				
Gene name	Role	Crop	Pathogen	Reference
ELICITOR AND EFFECTOR RECOGNITION RECEPTOR GENES (*ELRR* and *ERR*)				
NtERF3	Induces hypersensitive-response-like cell death	Tobacco	Tobacco mosaic virus	(Ogata *et al.*, 2012)
TiERF1	Mediates resistance through ethylene-dependent pathway	Wheat	*Rhizoctonia cerealis*	(Chen *et al.*, 2008)
TaPIE1	Regulates ethylene-dependent defense response	Wheat	*Rhizoctonia cerealis*	(Zhu *et al.*, 2014)
BOTRYTIS SUSCEPTIBLE 1 (BOS1)	Mediates ROS signals and regulates JA signaling pathway	Arabidopsis	*Botrytis cinerea, Alternaria brassicicola*	(Mengiste *et al.*, 2003)
TaMYB4	Induces defense response	Wheat	*Puccinia striiformis f. sp. tritici*	(Al-Attala *et al.*, 2014)
TaMYB30	Regulates very-long-chain fatty acids biosynthesis	Tobacco	*Pseudomonas syringae pv. tabaci*	(Raffaele *et al.*, 2008)
TaNAC4	Transcriptional activator	Wheat	*Puccinia striiformis f. sp. tritici*	(Xia *et al.*, 2010)
TaPIEP1	Activation of ET/JA-dependent defense genes	Wheat	*Bipolaris sorokiniana*	(Dong *et al.*, 2010)
OTHER REGULATORY GENES				
eIF2	Required for innate immunity	Wheat	*Puccinia striiformis f. sp. tritici*	(Zhang *et al.*, 2013)
TaHIR1 and TaHIR3	Induces hypersensitive response	Wheat	*Puccinia striiformis f. sp. tritici*	(Duan *et al.*, 2013)
TaNPSN SNARE	Vesicle-mediated resistance	Wheat	*Puccinia striiformis f. sp. tritici*	(Wang *et al.*, 2014a)
OsBIDK1	Diacylglycerol kinase activity	Tobacco	Tobacco mosaic virus, *Phytophthora parasitica var. nicotianae*	(Zhang *et al.*, 2008)
TaMCA4 (metacaspase 4)	Induces programmed cell death	Wheat	*Puccinia striiformis f. sp. tritici*	(Wang *et al.*, 2012)

B. Resistance-related metabolite (*RRM*) and resistance-related protein (*RRP*) biosynthetic genes involved in biotic stress resistance in plants

Gene name	Associated metabolites/ proteins	Crop	Pathogen	Reference
GENES BIOSYNTHESIZING *RRP*				
Dahlia merckii defensin (DmAMP1)	Defensin	Rice	*Magnaporthe oryzae, Rhizoctonia solani*	(Jha *et al.*, 2009)
CABPR1	Pathogenesis-related protein 1	Tobacco	*Phytophthora nicotianae, Ralstonia solanacearum, Pseudomonas syringae pv. tabaci.*	(Sarowar *et al.*, 2005)
CALTPI and CALTPII	Lipid transfer protein	Tobacco	*Phytophthora nicotianae Pseudomonas syringae pv. tabaci*	(Sarowar *et al.*, 2009)
SN1	Potato antimicrobial peptide	Wheat	*Gaeumannomyces graminis var. tritici*	(Rong *et al.*, 2013)
Lactoferrin	Broad-spectrum antimicrobial peptide	Wheat	*Fusarium graminearum*	(Han *et al.*, 2012)
Chitinase and β-1,3 glucanase	PR protein	Wheat	*Fusarium graminearum*	(Anand *et al.*, 2003)
NaD1 and NaD2	Class-I and -II defensin protein	Oats	*Puccinia spp.*	(Dracatos *et al.*, 2014)
Hpa1Xoo	Harpin protein	Cotton	*Verticillium dahliae*	(Miao *et al.*, 2010)
GENES BIOSYNTHESIZING *RRM*				
CYP71Z2	Phytoalexins	Rice	*Xanthomonas oryzae pv. oryzae*	(Li *et al.*, 2015)
Lipoxygenase (LOX)	Jasmonic acid, Methyl jasmonate	Maize	*Fusarium verticillioides*	(Christensen *et al.*, 2014)
Allene oxide synthase (AOS)	Jasmonic acid, Methyl jasmonate	Rice	*Magnaporthe grisea*	(Mei *et al.*, 2006)

(*Continued*)

Table 1. (Continued)

A. Regulatory genes (*R*) imparting biotic stress resistance in plants				
Gene name	Role	Crop	Pathogen	Reference
ELICITOR AND EFFECTOR RECOGNITION RECEPTOR GENES (*ELRR* and *ERR*)				
Indole glycerol phosphate lyase	DIMBOA glucoside DIMBOA, DIBOA	Maize	*Setosphaeria turcica*	(Ahmad *et al.*, 2011)
Callose synthase (PMR4)	Callose	Barley	*Blumeria graminis f. sp. hordei*	(Blümke *et al.*, 2013)
Linalool synthase	Linalool	Rice	*Xanthomonas oryzae pv. oryzae*	(Taniguchi *et al.*, 2014)
Resveratrol synthase (VST1 and VST2) pinosylvin synthase (PPS)	Resveratrol and pinosylvin-like compounds	Wheat	*Puccinia recondita f. sp. tritici*	(Serazetdinova *et al.*, 2004)
PinA and PinB	Puroindolines	Rice	*Magnaporthe oryzae, Rhizoctonia solani*	(Krishnamurthy *et al.*, 2001)
Squalene synthase (SQS)	Terpenoids: squalene and withanolides	*Withania somnifera*	*Botrytis cinerea*	(Singh *et al.*, 2015)
Agmatine coumaroyl transferase (TaACT)	p-coumaroylagmatine p-coumaroylputrescine	Wheat	*Fusarium graminearum*	(Kage and Kushalappa, 2015)
Agmatine coumaroyl transferase (ACT)	p-coumaroylagmatine, feruloylagmatine, p-coumaroylputrescine, feruloylputrescine	Arabidopsis	*Alternaria brassicicola*	(Muroi *et al.*, 2009)
Cinnamoyl alcohol dehydrogenase (CAD)	G and S lignin monomers	Arabidopsis	*Pseudomonas syringae pv. Tomato*	(Tronchet *et al.*, 2010)
Tyrosine decarboxylase (TyDC)	Feruloyltyramine Caffeoyltyramine Feruloyloctopamine	Potato	*Phytophthora infestans*	(Yogendra *et al.*, 2015b; Yogendra *et al.*, 2014)
Tyramine hydroxycinnamoyl transferase (THT)	Feruloyltyramine Caffeoyltyramine Feruloyloctopamine	Potato	*Phytophthora infestans*	(Yogendra *et al.*, 2015b; Yogendra *et al.*, 2014)
Cinnamoyl-CoA reductase (CCR)	Hydroxycinnamaldehydes (Coniferaldehyde)	Arabidopsis	*Xanthomonas campestris pv. Campestris*	(Lauvergeat *et al.*, 2001)
Caffeic acid/5-hydroxyferulic acid O-methyltransferase (COMT)	Sinapaldehyde Sinapyl alcohol,	Tobacco	*Tobacco mosaic virus (TMV)*	(Maury *et al.*, 1999)
L-phenylalanine ammonia lyase (PAL)	trans-Cinnamic acid	Rice	*Magnaporthe oryzae*	(Giberti *et al.*, 2012)

ELRR = elicitor recognition receptor; ERR = effector recognition receptor; PHR = phytohormone; MAPK = mitogen-activated protein kinase; TF = transcription factor; RRM = resistance-related metabolite; RRP = resistance-related protein; *R* = hierarchy of resistance genes that produce regulatory proteins, RRMs, and RRPs.

LRR) class of immune receptors, which in turn trigger downstream genes to induce hypersensitive response (Boller and Felix, 2009; Du *et al.* 2015). Broad-spectrum, race-non-specific and common to Phytophthora and Pythium species, elicitors called elicitins are recognized by RLPs (ELR) in potato triggering quantitative resistance (Du *et al.*, 2015). Approximately 615 RLKs have been reported in Arabidopsis (Boller and Felix, 2009; Dodds and Rathjen, 2010). Extracellular ligand-binding domain activates the intracellular kinase domain leading to phosphorylation of substrates and signal transduction. Bacteria produce cell wall lipopolysaccharides which are recognized by a surface-localized lectin S-domain receptor kinase (Macho and Zipfel, 2015). Fungi produce cell wall chitins that are recognized by a lysine motif (lysM) domain containing the *RLK1* gene, the chitin elicitor receptor kinase (CERK1) in Arabidopsis and rice, which in turn regulates TFs that regulate R_{RRM} genes to biosynthesize

RRMs that reinforce cell walls (Bashline *et al.*, 2014; Macho and Zipfel, 2015; Miya *et al.*, 2007) (Figure 1). Necrotrophs and hemibiotrophs, and at advanced stages of infection the biotrophs, produce several enzymes (elicitors), such as cutinases, xylanase, cellulases, pectin lyases, and laccases to break down the host cell wall, which releases DAMP (plant signal molecules) (Boller and Felix, 2009; Pendleton *et al.*, 2014). The host damage releases membrane lipids that activate a cascade of downstream genes prompted by phospholipases (PLs): PL-A activate jasmonic acid (JA), PL-C activate ion channels, and PL-D activate enzymes to produce phosphatidic acid, which activates MAPKs and oxidative bursts through NADPH oxidase controlled by R_{RRP} gene (Ruelland *et al.*, 2015). Oligogalacturonides, the plant signal molecules released from the breakdown of pectins in plant cell wall by *Botrytis cinerea* trigger phytohormones leading to the production of NADPH oxidase (RRP) and callose (RRM) in
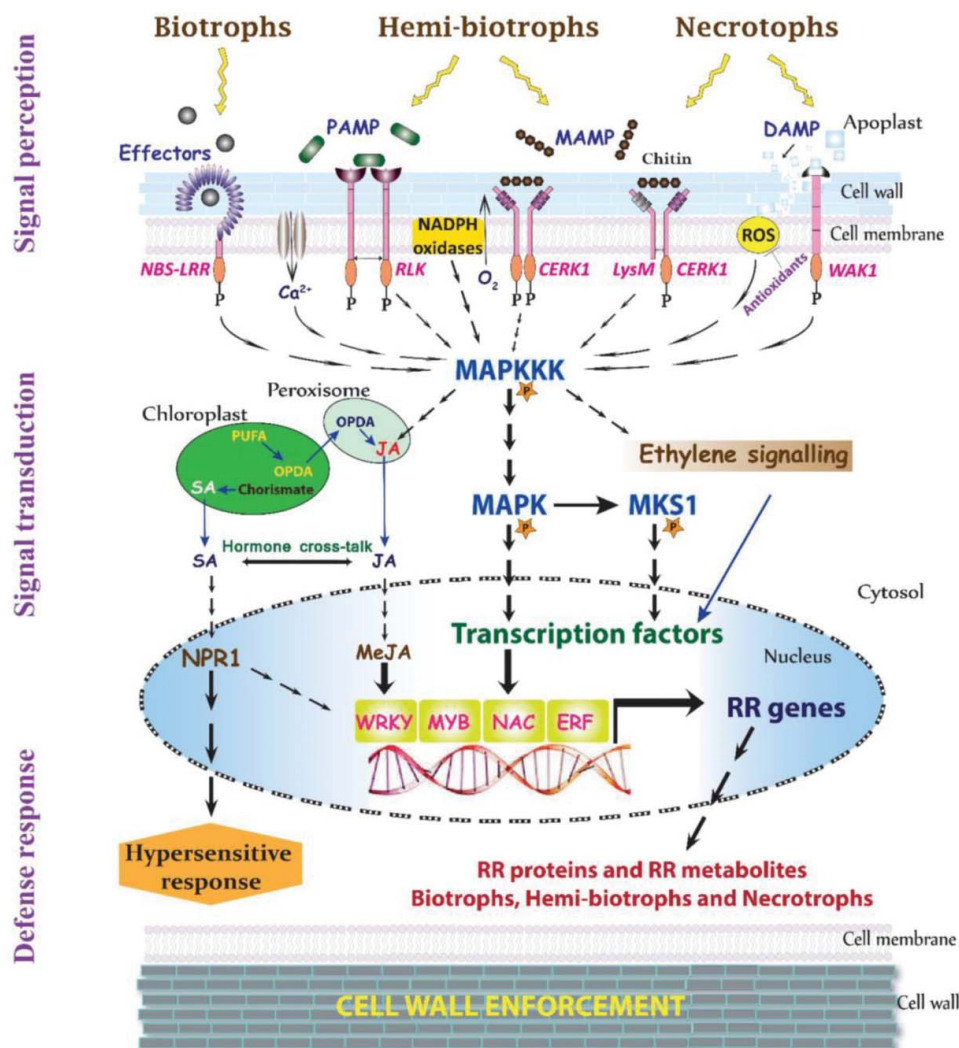
Figure 1. Snapshot of key players involved in plant-pathogen interaction. Plants face continuous challenges from several biotrophs, hemibiotrophs, and necrotrophic pathogens, which often attack and propagate in apoplastic space of plant tissues. Pathogens in general produce elicitors (former: PAMP/MAMP), except for specialized pathogens which also produce effectors. Plants recognize these elicitors/effectors and mount an immune response, by triggering a hierarchy of *R* genes (elicitor recognition receptor (*ELRR*), effector recognition receptor (*ERR*), phytohormone (*PHR*), mitogen-activated protein kinase (*MAPK*), transcription factor (*TF*)), eventually to produce resistance-related (RR) metabolites (RRMs) and proteins (RRPs), that directly supress the pathogen advancement. The elicitors are recognized by host membrane-localized ELRR (former: PRR), while the effectors are recognized by ERR (former: PRR produced by *R* genes). For example, effectors produced by biotrophs are often recognized by NBS-LRR proteins, leading to hypersensitive response via MAPK/SA/NPR1 pathway. On the other hand, elicitors such as chitins produced mainly by hemibiotrophs and necrotrophs are perceived by receptor-like kinases (RLK) and LysM domain chitin elicitor receptor kinase (CERK1), respectively, to activate downstream defense response through MAPK kinase kinase (MAPKKK) pathway. Necrotrophs produce elicitors such as enzymes and toxins, which damage the plant cell walls accumulating cell wall fragments and contents (Plant elicitors plant signal molecules; former: DAMPs), which activate plant defense response through wall-associated receptor kinases (WAKs). Concurrently, several secondary messengers such as calcium ions, reactive oxygen species (ROS), and plant hormone-mediated defense pathways (Ethylene, SA, and JA) are activated following biotic stress, which also trigger downstream genes resulting in hypersensitive response or reduced susceptibility. Overall, the signal perceived by receptor kinases are transmitted efficiently through cytosolic protein kinases such as MAPKKK pathway, to activate an array of plant transcription factors (WRKY, MYB, NAC, and ERF), which regulate several *R* genes to produce RRPs and RRMs. These RMs are phytoanticipins and phytoalexins, or their conjugate products that are deposited to enforce the secondary cell wall, thus containing the pathogen to initial infection area.

Arabidopsis (Galletti *et al.*, 2008; Łaźniewska *et al.*, 2012). Several necrotrophic and some hemibiotrophic pathogens produce toxins that not only act as effectors at low concentrations, activating downstream genes, but also inhibit plant defense mechanisms at high concentrations, facilitating pathogen advancement in the host (Boller and Felix, 2009; Gunnaiah and Kushalappa, 2014; Kabbage *et al.*, 2015; Mengiste, 2012).

B. Phytohormone (PHR) genes and regulation of downstream genes

The plant receptor genes (*ELRR/ERR*), following perception of elicitors/effectors, activate phytohormones that may bind to nuclear proteins with specific domains, such as the F-box, to activate downstream regulatory and R_{RM} genes (Lumba *et al.*, 2010). Several phytohormones are activated by receptor proteins, the most common of which are salicylic acid (SA) and jasmonic acid (JA) (De Bruyne *et al.*, 2014; Kazan and Lyons, 2014; Pieterse *et al.*, 2012). While SA is mainly involved in resistance to biotrophs, methyl JA and ethylene (ET) play a significant role in resistance to necrotrophic pathogens. SA, after being sensed by the transcription cofactor NPR1, moves into the nucleus where it modulates expression of regulatory and R_{RM} genes (Furniss and Spoel, 2015). JA, biosynthesized by allene oxide synthase (*StAOS2*), is associated with resistance in potato to late blight (Pajerowska-Mukhtar *et al.*, 2008). ET influences the TF ORA59 in Arabidopsis and regulates the production of hydroxycinnamic acid amides (HCAAs), increasing cell wall thickness, which confers resistance to *B. cinerea* (Lloyd *et al.*, 2011). ET in tomato regulates biosynthesis of tyramine hydroxycinnamoyl transferase (THT) to produce HCAAs acting against Cladosporium and Pseudomonas (Etalo *et al.*, 2013).

C. Mitogen-activated protein kinase (MAPK) genes and regulation of downstream genes

The MAPKs, activated by receptor genes, activate other MAPKs (Cristina *et al.*, 2010). In Arabidopsis infection by *B. cinerea*, receptors activate MAPKs that phosphorylate other MPK3/MPK6, which then phosphorylate WRKY33 leading to the biosynthesis of the phytoalexin camalexin (Mao *et al.*, 2011). MPK4 phosphorylation upon *Pseudomonas syringae* infection of Arabidopsis, released MKS1 and WRKY33, which induced the biosynthesis of camalexin (Rushton *et al.*, 2010). In rice, *OsMKK4-OsMPK4/MPK6* play crucial roles in regulating the biosynthesis of diterpenoid- and phenylpropanoid-derived phytoalexins and also lignins in response to a fungal chitin elicitor of *M. oryzae* (Kishi−Kaboshi *et al.*, 2010). In maize following *Fusarium verticillioides* infection, brassinosteroid-insensitive-1-associated receptor kinase 1 (BAK1) and homologs of *AtMKK4* were associated with ear rot resistance (Lanubile *et al.*, 2014).

D. Transcription factor (TF) genes and regulation of resistance metabolite genes

TFs play a pivotal role in biotic stress resistance by directly regulating downstream R_{RM} genes, and thus are excellent candidates in breeding for stress resistance (Alves *et al.*, 2014; Kou and Wang, 2012; Rushton *et al.*, 2010; Xu *et al.*, 2011). More than 2000 TFs have been reported in Arabidopsis. Six major families of TFs involved in plant defense are the basic leucine zipper containing domain proteins (bZIP), amino-acid sequence WRKYGQK (WRKY), myelocytomatosis-related proteins (MYC), myeloblastosis-related proteins (MYB), Apetala2/ET-responsive element-binding factors (AP2/EREBP), and no apical meristem/Arabidopsis transcription activation factor/Cup-shaped cotyledon (NAC) (Alves *et al.*, 2014). Phosphorylation of MAPK activates TFs by binding to the D site to then translocate into the nucleus (Whitmarsh, 2007). A TF can bind to itself, other TFs, or to several downstream R_{RM} genes in a specific metabolic pathway; leading to enhanced production of specific resistance metabolites (RM) (Mao *et al.*, 2011; Rushton *et al.*, 2010; Shan *et al.*, 2015). TF WRKY33 positively regulates resistance to necrotrophic pathogen *B. cinerea* through activation of tryptophan-derived camalexin biosynthesis in Arabidopsis (Ahuja *et al.*, 2012; Mao *et al.*, 2011). The overexpression of *VvWRKY1* induced a cinnamoyl alcohol dehydrogenase and a caffeic acid O-methyl transferase gene in grape vines, providing higher resistance to downy mildew (Marchive *et al.*, 2013) and the transcriptional activation of *StWRKY1* by heat shock protein (sHSP17.8)-induced phenylpropanoid genes in potato conferring resistance to late blight (Yogendra *et al.*, 2015a). In plants, a battery of NAC and MYB TFs activate secondary cell wall formation based on lignin monomers (Nakano *et al.*, 2015). WRKY29, a JA-responsive TF, was expressed only in *F. graminearum*-resistant genotype, Wangshuibai, but not when the QTL-Fhb1 region was deleted (Xiao *et al.*, 2013).

E. Resistance-related protein (RRP) and resistance-related metabolite (RRM) biosynthetic genes

The RRP and RRM directly suppress pathogens and are biosynthesized by resistance (R_{RRP}, R_{RRM}) genes (Table 1). These RRP and RRM are either constitutive (RRC), present before the pathogen invasion, or induced (RRI), induced following pathogen invasion. The amount of proteins and metabolites produced depends not only on the functional R_{RP} and R_{RM} genes, but also on the hierarchy of functional regulatory R genes that regulate them. The resistance related proteins (RRP) are the pathogenesis-related (PR) proteins that suppress pathogens, detoxify toxins or virulence factors produced by pathogens and prevent pathogen advancement by enforcing cell walls (Egorov and Odintsova, 2012; Łazniewska *et al.*, 2012). The resistance related metabolites (RRM) may be antimicrobial, such as

phytoanticipins and phytoalexins, or may form complex conjugates that are deposited to reinforce cell walls and suppress pathogen progress (Boller and Felix, 2009; Nawrot et al., 2014; Yogendra et al., 2014). Polymorphisms in introns, exons, and promoter regions, especially in the domain sequence, of these hierarchy of R genes determine the functionality of the proteins/enzymes produced, and thus the amount of proteins (RRP) and metabolites (RRM) biosynthesized (Eudes et al., 2014; Krattinger et al., 2009; Pushpa et al., 2014; Yogendra et al., 2015b; Yogendra et al., 2014). Thus, the amount of RRP or RRM biosynthesized by an R gene is significantly controlled by a hierarchy of regulatory R genes, especially the TFs, activated following the perception of elicitors/effectors. The resistance, both qualitative and quantitative, in plants is due to the cumulative effects of RRP and RRM biosynthesized by R_{RRP} and R_{RRM} genes, respectively, which in turn are affected by regulatory R genes that can regulate several R_{RRP} and R_{RRM} genes. These defense compounds are generally delivered to the site of infection in vesicles by several transporters, such as ABC and Arabidopsis PEN3 transporters (R genes) (Frescatada-Rosa et al., 2015).

IV. Resistance-related (RR) proteins and metabolites

A. *Resistance-related proteins (RRPs) and the mechanisms of pathogen suppression*

Following pathogen invasion plants induce several proteins (IRP), which are commonly known as PR proteins and about 17 of their families have been reported (Golshani et al., 2015; Van Loon et al., 2006). The PR proteins that are RRP include those with antimicrobial, toxin-degrading, and cell wall enforcing properties (Nawrot et al., 2014). PR proteins, β-1-3-endoglucanases (PR-2) and endochitinases (PR-3, 4, 8, and 11), break down pathogen cell walls (Jach et al., 1995). Chitinases breakdown chitin cell wall of fungi, β-1-3-glucanases break down cell wall glucans of bacteria and Chromista (Van Loon et al., 2006). PR peptides (molecular weight of <10 kDa) family more specifically proteinase inhibitors (PR-6), defensins (PR-12), thionins (PR-13), and lipid transfer proteins (PR-14) have broad antibacterial and antifungal activities (Sels et al., 2008). Members of PR-1 and thaumatin-like PR-5 families have resistance against Oomycetes (Van Loon et al., 2006). PR-7 is an endoproteinase, which helps in microbial cell wall cessation in tomato (Jordá et al., 2000).

Several hemibiotrophic and necrotrophic pathogens produce toxins that are peptides or metabolites, which act as elicitors inducing hypersensitive response at low concentrations and necrosis at high concentrations (Boller and Felix, 2009; Karlovsky, 1999). The toxic metabolites such as deoxynivalenol (DON) produced by *F. graminearum* in wheat and barley is a pathogen virulence factor, which is glycosylated by DON-3-glucosyl transferase gene, converting toxic DON to less toxic DON-3-glycosides, thus reducing further spread of pathogen from initial infection (Schweiger et al., 2010). Some toxins produced by pathogens are transported by ABC transporter proteins, such as pleotropic drug resistance transporters, to store them in vacuoles (Kang et al., 2011; Walter et al., 2015). Hydroxyproline-rich glycoproteins, called extensins, are deposited along with lignin monomers, to thicken the cell walls of Arabidopsis against *P. syringae* (Łaźniewska et al., 2012).

B. *Resistance-related metabolites (RRM) and the mechanisms of pathogen suppression*

RRMs called phytoanticipins are constitutively (RRC) produced in growing plants and are generally stored in trichomes, oil glands, and epidermal cell layers as nontoxic glycosides, while the toxic forms are released following simple hydrolysis. Plants produce thousands of phenols, flavonoids, terpenes, fatty acids, and alkaloids that are antimicrobial. Resistance metabolites may also be biosynthesized *de novo* following pathogen invasion; these are commonly known as phytoalexins (RRI) (Table 1) (Ahuja et al., 2012; Pedras and To, 2015; Piasecka et al., 2015). Resistance depends not only on the amount of metabolite biosynthesized by the plant, but also on the antimicrobial property of a given metabolite (Piasecka et al., 2015). These phytoalexins, in hundreds, are biosynthesized by R_{RRM} genes in various specific metabolic pathways (Figure 2) (Ahuja et al., 2012). *Phenylpropanoids and flavonoids*: isoflavonoids, isoflavones, pterocarpans, isoflavans, coumestans, arylbenzofurans, and stilbenes; *terpenes*: monoterpene, sesquiterpene, carboxylic sesquiterpene, and diterpene families; *indole*: camalexin (Jeandet et al., 2014; Kang et al., 2014; Yamamura et al., 2015). The pathogens also try to neutralize the effect of these phytoalexins by converting them to less toxic oxidized forms or conjugate with glycosides through production of enzymes (Jeandet et al., 2014).

Primary cell walls produced by cellulose and pectins are constitutively enforced by the deposition of secondary metabolites (RRC) (Bashline et al., 2014; Eudes et al., 2014; Nakano et al., 2015). In addition, following pathogen invasion, more secondary metabolites are induced (RRI) and these form complex polymers that are deposited in xylem vessels to enforce cell walls
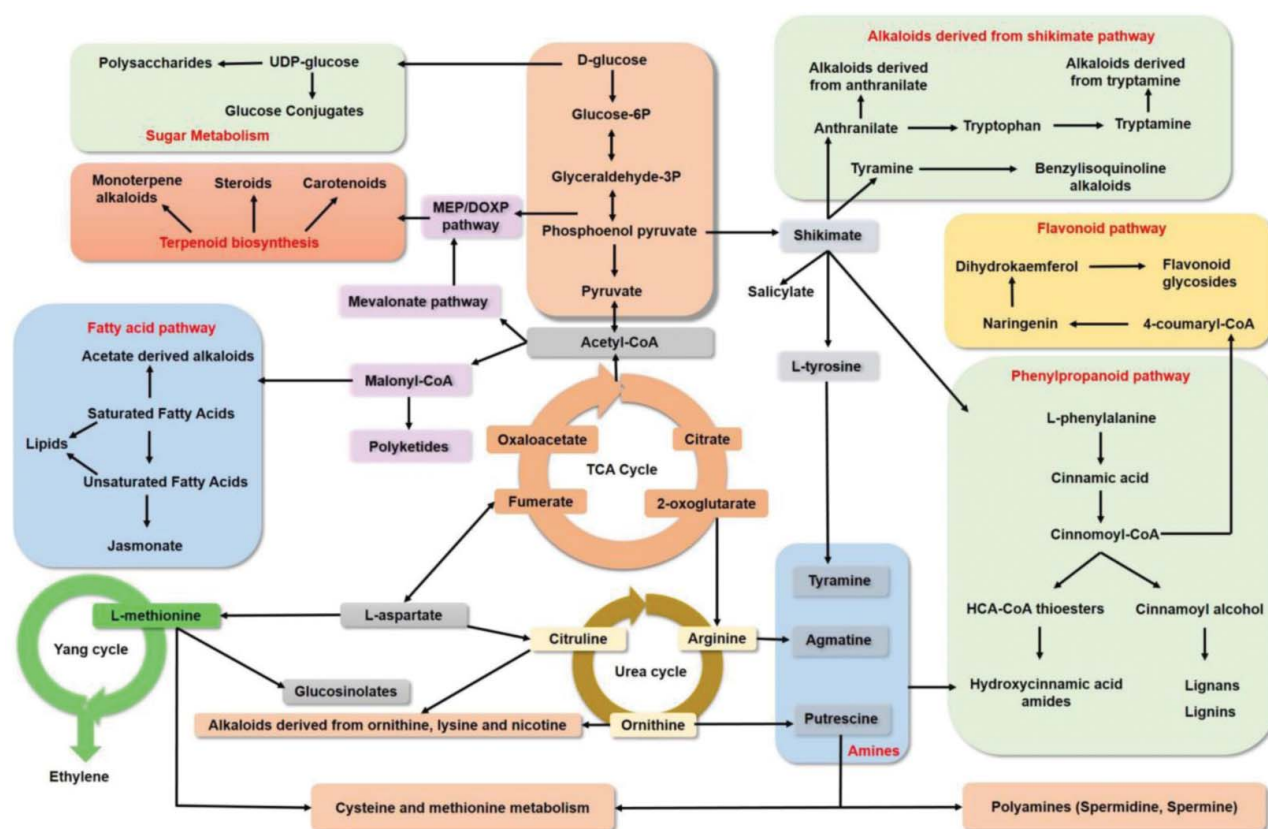
Figure 2. Satellite metabolic pathways, involved in the biosynthesis of RRMs by plants, in response to biotic stress. These resistance metabolites are biosynthesized by the catalytic proteins that are coded by the plant R_{RRM} genes. The biosynthesis of RRMs in a plant is controlled by a hierarchy or several hierarchies of R genes, which may have regulatory or RRM production roles.

(Gunnaiah et al., 2012; Wang et al., 2014b; Yogendra et al., 2015a). The conjugated complex metabolites, not degraded by the enzymes produced by most pathogens, are produced in the phenylpropanoid, flavonoid, fatty acid, and alkaloid metabolic pathways (Figure 2) (Nakano et al., 2015; Yogendra et al., 2015b). These play a significant role in plant resistance; *Lignin*: These are three-dimensional phenolic heteropolymers resulting from the oxidative coupling of three p-hydroxycinnamoyl (p-coumaryl, coniferyl, and sinapyl) alcohols. The cross-coupling reaction of monolignols forms p-hydroxyphenyl, guaiacyl, and syringyl lignins. These, and also lignans, are deposited to enforce secondary cell walls, thus preventing pathogen spread mainly through stem and rachis of inflorescence (Fernández−Pérez et al., 2015; Niks et al., 2015). *Hydroxycinnamic acid amides (HCAAs)*: Hydroxycinnamic acid amides are produced as polymers of amines and hydroxyphenols, in several combinations (Figure 3) (Dong et al., 2015; Kusano et al., 2015; Wen et al., 2014; Yogendra et al., 2015a). They are deposited as secondary cell walls to prevent the advance of pathogens as proved in wheat against *F. graminearum* (Gunnaiah et al., 2012), in tomato against *P. syringae*

(López-Gresa et al., 2011), in Arabidopsis against *B. cinerea* (Lloyd et al., 2011), and in potato against late blight (Yogendra et al., 2015a). *Callose*: A β-1,3-glucan polymer is deposited around the invading hyphae of the biotroph *Blumeria graminis* in barley and wheat to form papillae leading to hypersensitive response or resistance against powdery mildew; this is quite common against several other biotrophs in other crops (Łaźniewska et al., 2012; Nedukha, 2015). *Kaempferol and quercetin glycosides*: Flavonol glycosides form a hard, crystalline structure as a physical barrier against pathogens. Kaempferol, quercetins, and their glycosylated forms prevent the spread of *F. graminearum* in barley (Bollina et al., 2010; Kumaraswamy et al., 2012) and *P. infestans* in potato (Fellenberg and Vogt, 2015; Pushpa et al., 2014; Yogendra et al., 2014). *Pectin-alkaloid*: Pectins are primary cell wall components and following pathogen invasion they conjugate with alkaloids and deposit to enforce secondary cell walls (Didi et al., 2015). *Cutin and wax*: These are polymers of fatty acids deposited on the cuticle and peridermal layers to prevent pathogen invasion (Andersen et al., 2015; Łaźniewska et al., 2012; Shi et al., 2013). *Suberin*: Suberins are polymers of polyaromatic, such as
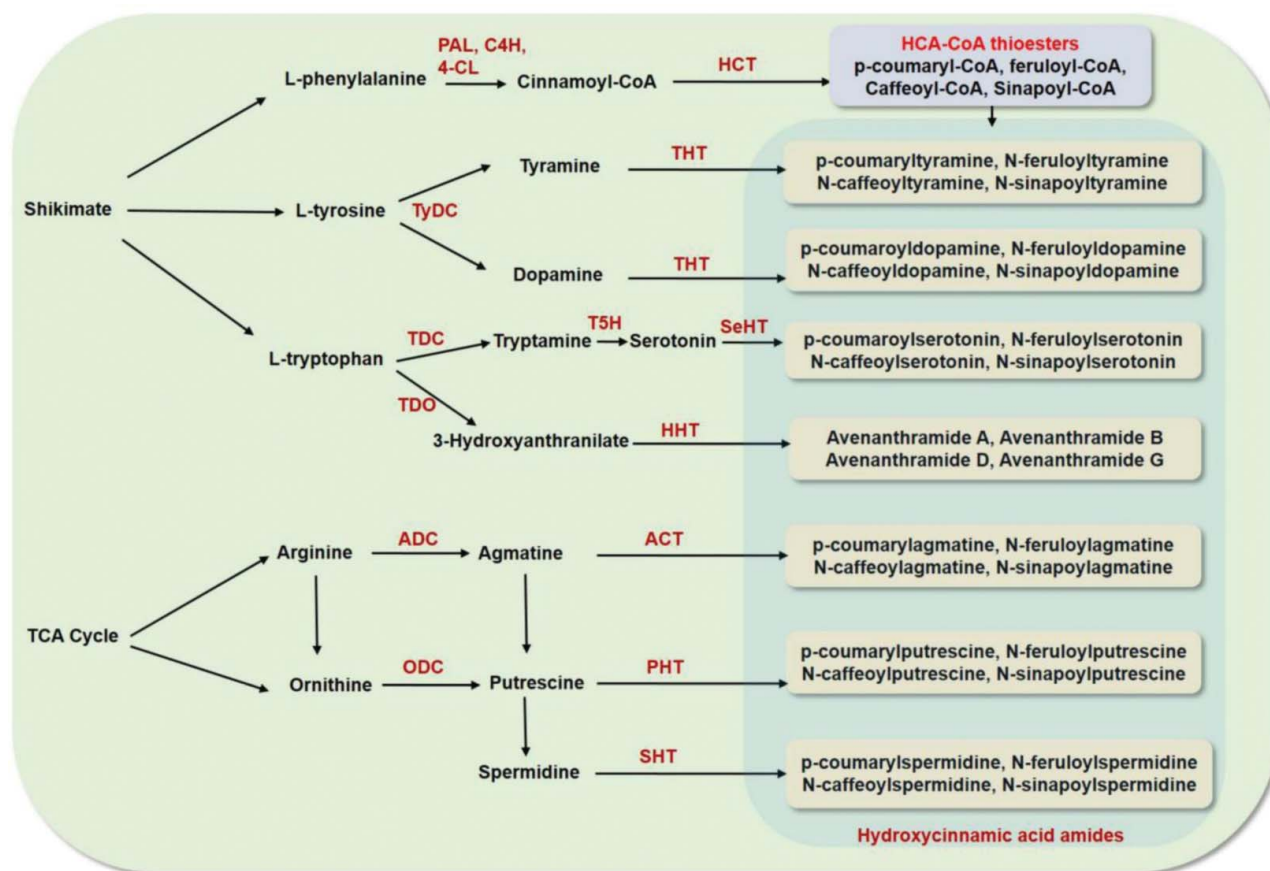
Figure 3. Proposed pathway of hydroxycinnamic acid amides biosynthesis by *R* genes. PAL, phenylalanine ammonia lyase; C4H, cinnamate 4-hydroxylase; 4-CL, 4-coumarate: CoA ligase; HCT, hydroxycinnamoyl transferase; TyDC, tyrosine decarboxylase; THT, tyramine hydroxycinnamoyl transferase; TDC, tryptophan decarboxylase; TDO, tryptophan 2,3-dioxygenase; T5H, tryptamine 5-hydroxylase; SeHT, Serotonin hydroxycinnamoyl transferase; HHT, hydroxyanthranilate hydroxycinnamoyl transferase; ADC, arginine decarboxylase; ACT, agmatine coumaroyl transferase; ODC, ornithine decarboxylase; PHT, putrescine hydroxycinnamoyl transferase; SHT, spermidine hydroxycinnamoyl transferase.

hydroxycinnamic acid, and polyaliphatic, such as ω-hydroxy acid, metabolites. They are deposited not only in periderm but also in xylem (Gunnaiah and Kushalappa, 2014; Vishwanath *et al.*, 2015; Yogendra *et al.*, 2014).

C. Metabolic pathways of resistance metabolite (RRM) biosynthesis

Plants produce more than 200 000 secondary metabolites. These are biosynthesized from glucose in specific metabolic pathways (Figure 2). Thus, the production of a metabolite and its amount depends on a network of functional genes (*R*), including receptors (*ELRR, ERR*), phytohormones (*PHR*), MAPKs (*MAPK*), TFs (*TF*), and resistance metabolite (*RRM*) genes. A nonfunctional gene in this chain, a missing link, can lead to reduced amount or complete absence of a metabolite. The amount of metabolites biosynthesized by R_{RM} gene thus

can be significantly influenced by the TFs that regulate them. A TF can bind to several R_{RM} genes thus affecting the abundances of several resistance metabolites. Similarly, a R_{RRM} gene can be regulated by more than one TF. TFs also can bind and regulate each other (Shan *et al.*, 2015). Thus, the metabolic pathway regulation is quite complex, requiring further research.

The resistance metabolites (RRM) identified in different pathosystems are (Table 1) *Shikimic acid pathway*: The biosynthesis of phenylalanine, tyrosine, and tryptophan leads to the production of phenylpropanoids, flavonoids, and some alkaloids. The production of cinnamic acid from phenylalanine and cinnamoyl-CoA leads to the production of phenylpropanoid metabolites, and 4-coumaroyl CoA leads to the production of flavonoid metabolites (Eudes *et al.*, 2014). The production of anthranilate leads to the production of some alkaloids. *Mevalonate pathway*: Acetyl-CoA leads to the production of terpenes, consisting of isoprene units forming

mono- di-, tri-, and sesquiterpenes (Tholl, 2015). *Fatty acid pathway*: Acetyl-CoA produces malonyl CoA which leads to the production of fatty acids and lipids (Ahuja *et al.*, 2012; Baetz and Martinoia, 2014; Grosjean *et al.*, 2015). *Polyamine pathway*: The biosynthesis of arginine leads to the production of putrescine, spermidine, and spermine (Dong *et al.*, 2015). *Glucocinolate pathway*: The biosynthesis of aspartate and methionine leads to the production of sulfur-containing compounds (Ahuja *et al.*, 2012; Bednarek, 2012). These also produce, in the Yang cycle, ET; which is a signaling molecule mainly involved in response to necrotrophic infection (Mengiste, 2012).

V. Gene (*R*) pyramiding based on genome editing

Hundreds of cultivars have been bred for each staple food crop such as wheat, rice, and potato in order to meet the demands for growing in niche climatic regions, food, feed, and bioproducts. For lack of disease resistance, some of the old cultivars, in spite of several good traits, are going out of production. Thus the cultivated crops in general lack genetic diversity. Natural as well as intentional hybridization and mutations caused the gain or loss of thousands of gene functions in cultivars and germplasm collections, thus a plethora of biotic stress resistance genes (*R*) are available for plant resistance improvement (Kage *et al.*, 2015; Palmgren *et al.*, 2015).

Several R_{ERR} genes have been pyramided in potato against late blight but the resistance is not durable, and the pathogen overcomes resistance by producing new effectors (Jacobsen, 2013). In these cultivars, the presence of functional R_{RM} and/or R_{RP} genes must be confirmed to guarantee production of resistance metabolites and/or resistance proteins, the end products that give resistance. A few quantitative resistance genes, such as *Lr34* in wheat against leaf rust (*Puccinia triticina*), *Yr36* in wheat against stripe rust (*Puccinia striiformis*), and *Pi21* in rice against blast (*Magnaporthe oryzae*), have been cloned and used successfully in breeding, though their mechanism of resistance are not yet completely understood (Niks *et al.*, 2015). Though the resistance in plants against pathogen stress is due to several plausible plant-pathogen gene interactions (Niks *et al.*, 2015), the resistance metabolites and resistance proteins that are biosynthesized by *R* genes, which in turn are activated by regulatory genes such as *ELRR*, *ERR*, *PHR*, *MAPK*, and *TF*, as reviewed here, play a major role in plant resistance. It is crucial to make sure that any candidate *R* gene selected for breeding has rest of the *R* gene team to ensure production of a given resistance biochemical that can directly suppress the pathogen. A cultivar may have a

complete hierarchy of these functional genes except for a missing link that is nonfunctional. Candidate genes, or missing links, with significant resistance effects, can be identified in germplasms based on several approaches (Chen *et al.*, 2014; Wen *et al.*, 2014) and these candidate genes can be DNA sequenced in commercial cultivars, and if nonfunctional, they can be replaced with functional candidate genes to improve resistance. Some of the regulatory genes, especially TFs, are excellent candidates, if found to be polymorphic in commercial cultivars: *TaWRKY45* in wheat QTL 2D, which regulates agmatine coumaroyl transferase (*TaACT*) and other genes to produce coumaroyl agmatine that are deposited to enforce cell walls, significantly suppressed the biomass of *F. graminearum* (Kage and Kushalappa, 2015). In potato, the *StWRKY1* gene regulates THT to produce N-feruloyltyramine and N-feruloyloctopamine (Yogendra *et al.*, 2015a). When these genes in the resistant plants were silenced not only the candidate metabolite abundances were significantly reduced but also the pathogen biomass and disease severity significantly increased, proving the resistance function of these genes. Based on our ongoing research, on candidate genes in the QTLs conferring resistance, these *TF* genes are excellent candidates to improve resistance in commercial cultivars.

Cisgenic transformation is the transfer or replacement of genes between sexually compatible genotypes. These genes must contain their own promoter, coding region, introns, and terminators (Jacobsen, 2013). A paradigm shift is now needed, from conventional and molecular breeding to genome editing, in order to replace these nonfunctional gene sequences in commercial cultivars with functional sequences. The cisgenic and intergenic gene pool can be explored to improve plants (Holme *et al.*, 2013; Zhan *et al.*, 2015). Among several DNA sequence replacement technologies available, the regularly interspaced short palindromic repeats (CRISPR-Cas9 system) are the most preferred for their simplicity to replace either based on agro-transformation or direct introduction to the protoplast (Shan *et al.*, 2014). The background DNA can be removed based on self-crossing. Preassembled CRISCR-Cas9 ribonucleoproteins have now enabled DNA-free genome editing in plants (Woo *et al.*, 2015). Cisgenics, unlike transgenics, face less regulatory challenges, as such transformations are expected to be similar to conventional breeding (Clasen *et al.*, 2015; Jones, 2015).

VI. Conclusion and future research

Resistance in plants against microbial stress is either qualitative or quantitative, but the mechanisms of

resistance are quite common, controlled by oligo- or polygenes. Plant receptors (ELRR, ERR), following perception of pathogen (elicitor, effector), trigger a hierarchy of regulatory genes (*PHR, MAPK,* and *TF*) that control expression of R_{RM} and R_{RP} genes, which biosynthesize resistance metabolites and resistance proteins that directly suppress pathogens. The hierarchy of these *R* genes with significant trait/resistance effect can be identified in world germplasm collections and used to replace the nonfunctional genes, the missing link, in commercial cultivars to improve resistance. The future research should focus on revealing the hierarchical link of genes involved in pathogen perception and further triggering of downstream regulatory, and R_{RRM} and/or R_{RRP}, genes that are responsible in plant to biosynthesize resistance metabolites and resistance proteins, both constitutive and induced, and biochemical and structural, which directly suppress pathogen, leading to resistance.

Acknowledgments

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