Front. Biol. 2017, 12(4): 258–270
DOI 10.1007/s11515-017-1460-4

REVIEW

Salicylic acid-mediated plant defense: Recent developments, missing links, and future outlook

Ian Arthur Palmer, Zhenhua Shang, Zheng Qing Fu (✉)

University of South Carolina, Department of Biological Sciences, University of South Carolina, Columbia, SC 29208, USA

BACKGROUND: Plant pathogens are responsible for many of history's greatest famines. Understanding how plants defend themselves against pathogens is crucial to preventing future famines. Salicylic acid (SA)-mediated plant defense is a key defense pathway, which plants use to defend against biotrophic and hemi-biotrophic pathogens. As a master regulator of SA-mediated plant defense, NPR1 interacts with TGA and WRKY transcription factor families, individual members of which positively or negatively regulate plant defense.
OBJECTIVE: In this review we describe the recent developments and predict future directions of research on the involvement of circadian rhythm-, autophagy-, and viral RNA silencing-related genes in SA-mediated plant defense on SA, on plant defense, the induction effects of PR proteins, and the mechanisms by which NPR1 regulates defense-related genes.
METHODS: We performed an extensive search of current and past literature using the PubMed, Google Scholar, and Google search engines. Our search terms included: "SA-mediated plant defense," and "NPR1 [AND] salicylic acid." Other search terms, wildcards, and Boolean operators were paired with "NPR1" or "plant defense" as needed to research more detailed information related to specific topics covered within this review. We also used Google to search for, "economic impact citrus greening," "aspirin," "Irish potato famine," and "rice blast," among other terms, to gather background information on the history and impact of plant diseases, and the historical use of aspirin.
RESULTS: Of 148 sources found, 132 were directly related to plant defense. The remaining sources are related to the historical and economic impact of plant diseases and the historical use and mechanism of action of aspirin or salicylate. All reviewed sources have been documented in the references section.
CONCLUSION: The topic of salicylic acid-mediated plant defense is broad, and new research is expanding our understanding of this topic quickly. In this review, we give a basic overview of the historical economic impact of plant diseases, and how an understanding of SA-mediated plant defense can prevent future famines. We provide a basic overview of plant defense, then discuss how SA acts as a defense signaling molecule.We discuss how SA regulates NPR1, which goes on to activate expression of SA-related genes including *PR* genes. Later, we discuss current research topics, including the role of NPR1 and SA in autophagy, circadian rhythmicity, viral gene silencing, SA biosynthesis, and SAR. We also discuss the potential roles of PR proteins, other SA binding proteins, WRKY and TGA family transcription factors, Elongator, and ER transport proteins in plant defense. Finally, we discuss the potential future routes that research into this topic could take, in order to further our understanding of role SA plays in plant defense.

Keywords salicylic acid, plant defense, SA-mediated defense

Introduction

Diseases caused by invading pathogens are a common problem for all species. Plant diseases caused by plant pathogens, such as fungi, bacteria, oomycetes, viruses and nematodes, are responsible for a substantial loss of crop yield each year. One well-known example is the potato late blight disease, caused by the oomycete pathogen *Phytophthora infestans* (Ó Gráda, 2007). Late blight is responsible for the infamous Great Irish Potato Famine, which lasted from 1845 to 1852, and resulted in the death of over one million people, and the emigration of another million (Ross, 2002). Another example is rice blast, caused by the fungus *Magnaporthe*

Received May 8, 2017; accepted June 27, 2017
Correspondence: Zheng Qing Fu
E-mail: zfu@mailbox.sc.edu

grisea (Talbot, 2003). Rice blast is estimated to destroy enough rice to feed 60 million people annually, and is now known to be present in 85 countries (Scardaci et al., 2016). Further, the citrus greening disease, also known as Huanglongbing, is caused by a psyllid-transmitted bacterial pathogen known as *Candidatus* Liberibacter spp. (Lin and Lin, 1956). This devastating disease recently appeared in the citrus fields of California, Mississippi, Louisiana, Georgia, Alabama, Florida, South Carolina, and Texas (Kunta et al., 2012). California alone boasts a citrus industry of $3.38 B, as of 2015, which is threatened if the pathogen continues to spread (U.S.D.A. and N.A.S., 2015). As of 2015, Florida produced only 96.8 million boxes of oranges, an eight percent reduction from the previous year, a 60% reduction from the 242 million boxes produced a decade ago (U.S.D.A. and N.A. S., 2015). The Florida citrus industry is a $10B industry that has been losing about $1B each year since 2005 due to citrus greening disease (Spreen, 2012).

To defend against these microscopic invaders, organisms have evolved different defense mechanisms to protect themselves. In plants, these mechanisms generally rely upon the successful detection of pathogens, followed by physiologic changes that result in increased defense against the invader. These changes include the formation and release of reactive oxygen species and other antibiotic substances, the deposit of molecules to strengthen the cell wall, and programmed cell death, known as the hypersensitive response (HR) (Glazebrook, 2005).

Plant defense mechanisms are generally classified into two tiers: MAMP-triggered immunity (MTI) and ETI (Effector-triggered immunity). MTI, also known as microbe-associated molecular pattern (MAMP)-triggered immunity is associated with the detection of highly conserved, signature, pathogen associated molecules known as microbe-associated molecular patterns (MAMPs), including flagellin, chitin, and elongation factor T_u, among others (Boller and Felix, 2009). ETI, is a more severe defense mechanism, and supplements MTI. ETI is associated with HR in resistant hosts, and it is triggered by direct or indirect recognition of pathogenic effector proteins by plant resistance (R) proteins (Tsuda and Katagiri, 2010), for example: the type III effector AvrR2 functions as a cysteine protease that cleaves the negative regulator of plant defense, RIN4. Recognition of degradation product of RIN4 by the resistance protein RPS2 activates ETI and triggers HR (Axtell et al., 2001; Mackey et al., 2003) (See Fig. 1). Activation of ETI will not only produce rapid cell death in the infection zone, but also induce the production of the plant defense hormone salicylic acid (SA), and activate systemic acquired resistance (SAR) in the entire plant (Fu and Dong, 2013; Wu et al., 2014).

SA is well known as a precursor of aspirin, the active ingredient of which is acetylsalicylic acid. Aspirin is among the oldest, cheapest, and most widely used medicines in human history; it is broadly used as fever-reducer, pain-reliever, and anti-inflammatory medicine (Myers, 2007). Studies have shown that long-term use of aspirin may reduce the risk of stroke, cardiovascular disease, and heart attack. In addition, non-acetylated salicylate shows effectiveness in treating type II diabetes (Goldfine et al., 2013). In humans, aspirin irreversibly inhibits cyclooxygenase 1 (COX-1) (DeWitt et al., 1990), and modifies the enzymatic activity of COX-2, both of which catalyze the production of prostaglandin H2 from arachidonic acid, involved in inflammation, and thromboxane A_2, involved in blood clotting (Preston et al., 1981; Smith et al., 1996). SA and its derivatives also inhibit IκB kinase (Yin et al., 1998), NF-κB (Kopp and Ghosh, 1994), and activate AMP-activated protein kinase (Hawley et al., 2012).

As one of the major plant hormones, SA plays a regulatory role in many physiologic processes, such as seed germination, storage, and fruit maturity (Raskin, 1992). In addition, SA plays roles in regulating flowering development, sex differentiation, stomatal movement, and photoperiod. SA is both required and sufficient to induce a defense response against pathogens (Raskin, 1992). Transgenic plants over-expressing the *NahG* transgene from *Pseudomonas putida*, encoding SA-degrading hydroxylase, have been proven to be more susceptible to a variety of pathogens (Delaney et al., 1994).

During pathogen infection, SA is synthesized in the chloroplast, primarily through the isochorismate pathway in *Arabidopsis*. Isochorismate synthases one and two (ICS1/2) are localized in the plastid, and ICS1 is responsible for the majority of SA accumulation in response to the presence of hemi- and biotrophic pathogens (Strawn et al., 2007; Fragnière et al., 2011). *Arabidopsis ics1* mutant plants are significantly reduced in SA level, and as a consequence, these mutants are more susceptible to pathogen infection.

In addition to inducing a local defense response, SA promotes systemic acquired resistance (SAR) after an invading pathogen is recognized (An and Mou, 2011). SAR protects the plant against further pathogen colonization by causing a systemic defense reaction including the production of pathogensis related (PR) proteins, phytoalexins, and the strengthening of cell walls. SA is also responsible for regulating these later responses to pathogenic invasion (Lu et al., 2016), and application of SA is sufficient to induce plant defense including SAR (Anand et al., 2008).

It was suggested that methyl salicylate (MeSA) is the mobile signal that can induce SAR in *Nicotiniana benthamiana.* MeSA moves through phloem from infected tissue to healthy tissue, acting as a long distance defense signal. MeSA is a gaseous product of SA, produced in infected tissue, which is converted back to SA in target tissues (Shulaev et al., 1997; Chen et al., 2003); however, MeSA does not seem to be a mobile defense signal in *Arabidopsis* (Attaran et al., 2009). Research indicates that *Arabidopsis* plants lacking salicylic acid methyltransferase fail to accumulate MeSA, but still

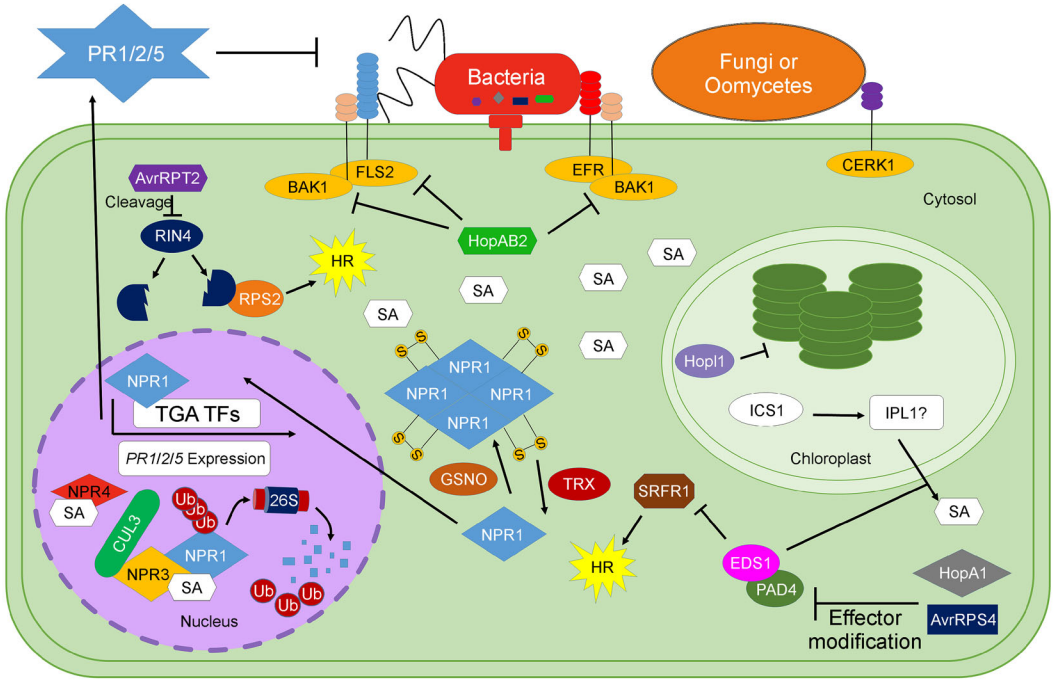

Figure 1 A model of SA-mediated plant defense. Biotrophic and hemi-biotrophic pathogens attempt to colonize plant tissue. After PRRs sense MAMPs, SA accumulates within the cell. SA is synthesized in the chloroplast by ICS1 and IPL1(?) through the isochorismate pathway. Pathogens inject effectors into the plant cell via the T3SS to interfere with MTI and SA biosynthesis. HopAB2, a pathogenic effector, binds BAK1, to inhibit its kinase activity and disrupt MAMP perception (Cheng et al., 2011). HopI1 remodels the chloroplast grana to interfere with SA biosynthesis (Jelenska et al., 2007). AvrRPT2 modifies a negative regulator of plant defense, RIN4. HopA1 and AvrRPS4 can modify PAD4 to inhibit SA biosynthesis. EDS1 can detect this interaction, inhibit SRFR1, a negative regulator of cell death, leading to HR. This modification of RIN4 is recognized by R protein RPS2, which triggers HR and ETI. In the cytosol, NPR1 is reduced from oligomer to monomer, facilitated by thioredoxin (TRX). In the absence of SA, S-nitrosoglutathione (GSNO) facilitates NPR1's oligomerization. NPR1 monomer moves to the nucleus, where it interacts with TGA transcription factors to induce *PR1/2/5* expression. After synthesis, the PR proteins move to the apoplast, where they inhibit pathogen colonization. When SA accumulates to a high level, NPR3 interacts with CUL3 as an adaptor to ubiquitinate NPR1. NPR4 is present in the nucleus, but only acts as a CUL3 adaptor to ubiquitinate NPR1 when SA level is low. The main function of NPR3 and NPR4 is to maintain optimum level of NPR1 protein during plant defense response. After polyubiquitination, NPR1 is degraded within the nucleus by the 26S proteasome. EDS1 forms a heterocomplex with PAD4. When EDS1 detects effector modification by AvrRPS4 or HopA1, it inhibits the activity of SRFR1, a cell death suppressor protein, which leads to HR. EDS1 also induces the production of SA in the presence of pathogens.

possess the ability to systemically accumulate SA and activate SAR (Attaran et al., 2009). *Arabidopsis* mutants that cannot respond to or synthesize SA cannot effectively induce SAR, and their basal defense is also compromised (Durrant and Dong, 2004). In addition to inducing defense, secreted SA acts as an intercellular antimicrobial agent against *Pseudomonas* spp. and fungal pathogens in *Arabidopsis* (Cameron and Zaton, 2004; Carviel et al., 2009; Carviel et al., 2014).

SA is important for defense against biotrophs and hemi-biotrophs, but is generally not effective against necrotrophic pathogens, because these pathogens are not impeded by cell death nor HR. The jasmonic acid and ethylene signaling pathways activate defenses against necrotrophic pathogens (Glazebrook, 2005).

Plants and plant pathogens are locked in an evolutionary arms race to develop more advanced proteins to enhance or subvert plant defense, respectively. EDS1 is a positive regulator of basal resistance to biotrophic pathogens (Wiermer et al., 2005), required by many *Arabidopsis* TIR-NB-LRR class R proteins to activate ETI (Feys et al., 2001). EDS1 is required for accumulation of SA in response to a pathogen (Parker et al.,1996), and it has been reported that the reduced levels of SA in *eds1* and *pad4* mutants results in increased susceptibility to pathogen infection (Falk et al., 1999; Jirage et al.,1999; Nawrath et al., 2002). In addition to EDS1, PAD4 also serves as a regulator of basal plant immunity. EDS1 forms heterocomplexes with PAD4 in the nucleus and cytoplasm, which are required for HR and pathogen resistance (Feys et al., 2001) (See Fig. 1). In addition to PAD4, EDS1 also interacts with SAG101 (SENESCENCE ASSOCIATED PROTEIN 101), which can form a ternary complex with EDS1 and PAD4, and plays a pivotal role in pathogen resistance (Feys et al., 2005; Zhu et al., 2011; Wagner et al., 2013). It is also demonstrated that EDS1 interacts with SRFR1 (SUPPRESSOR OF RPS4-

RLD1), which is a tetratricopeptide repeat containing a negative regulator of ETI (Kim et al., 2009; Kwon et al., 2009) (See Fig. 1). EDS1 also interacts with TIR-NB-LRR proteins RPS4 and RPS6, and the interactions between them are disrupted in the presence of AvrRps4 and HopA1 respectively (Bhattacharjee et al., 2011; Heidrich et al., 2011) (See Fig. 1).

PBS3 is a member of the GH3 family of acyl-adenylate/thioester-forming enzymes, which when mutated, causes SA to fail to accumulate, no induction of *PR1* defense gene, and increased pathogen susceptibility (Nobuta et al., 2007). EDS1, PBS3, and PAD4 proteins are critical to SA-mediated plant defense, and likely targets for pathogen effectors.

Recent developments in SA-mediated plant defense

SA biosynthesis

In addition to the primary ICS1/2 SA biosynethesis pathway, another less often used, redundant pathway exists for SA synthesis: the phenylalanine ammonia-lyase (PAL) pathway. This pathway converts phenylalanine into trans-cinnamic acid, then to benzic acid, and finally to salicylic acid (Mauch-Mani and Slusarenko, 1996). Basal levels of SA vary widely between plant species, with up to 100-fold differences recorded between species (Raskin et al., 1990). In addition, most of the SA produced by plants is glycosylated or methylated or both. Glycosylation at the hydroxyl group yields SA 2-O-β-D-glucoside (SAG), which is speculated to serve as an inactive storage form of SA that can be released from the cell's vacuole as needed (Dean and Mills, 2004; Dean et al., 2005).

In *Arabidopsis*, the isochorismate pathway is the main biosynthetic pathway for pathogen induced SA; however, current research suggests that the PAL pathway may play a more important role in SA biosynthesis in other plants. Shine, et al., examined the PAL pathway in soybean. They discovered that, unlike *Arabidopsis*, knocking out proteins in either the PAL or ICS pathways caused a similar reduction in defense response to invading pathogens. This research indicates that both pathways are equally important to plant defense (Shine et al., 2016). Huang et al. (2010) generated a *pal1/2/3/4* quadruple mutant *Arabidopsis*, and found that this mutant could accumulate only substantially reduced levels of SA, and was much more susceptible to *Pseudomonas syringae* than its wild type counterparts, further suggesting an overlapping role of *PAL* genes in defense. More research is needed to determine if the PAL pathway plays a role in pathogen-induced SA biosynthesis in *Arabidopsis* and in other plants.

Redox and post-transcriptional regulation of NPR1

The SA signaling pathway is regulated by NPR1, which co-activates 95% of SA-related defense genes (Pajerowska-Mukhtar et al., 2013). After pathogen infection, SA accumulates in the cytosol of infected cells, altering the redox state of those cells (Mou et al., 2003). This altered redox state causes NPR1 to dissociate from an oligomeric state to a monomeric state, and move to the nucleus (Tada et al., 2008). In this state, NPR1 interacts with TGA-bZIP transcription factors in the nucleus. This leads to the expression of several SA-dependent genes including *PR1/2/5* (Zhang et al., 1999; Zhou et al., 2000) (Fan and Dong, 2002). Depending on the level of SA present, NPR1 is poly-ubiquitinated by CUL3, with NPR3 and NPR4 acting as adaptors (Fu et al., 2012), and degraded by the 26S proteasome to prevent the activation of immune responses in naïve cells without infection or SA (Spoel et al., 2006). NPR1's degradation in the nucleus is dependent on its interaction with NPR3 and NPR4, both of which only bind NPR1 when a high level or a low level of SA is present, respectively (Fu et al., 2012). SA-mediated plant defense is, therefore, biphasic. NPR1 may only accumulate in the nucleus at high level when a moderate level of SA is present (Fu et al., 2012) (See Fig. 1). Additionally, the phytohormone abscisic acid (ABA) and SA antagonistically affect NPR1 levels during pathogen infection. While SA can prevent NPR1's proteasome-mediated degradation via CUL3, ABA promotes this degradation (Ding et al., 2016). Indeed, a deficiency of ABA has been found to cause constitutive *PR* gene expression (Mosher et al., 2010), suggesting that ABA can prevent defense gene activation in the absence of a pathogen infection.

As a transcriptional co-activator, the nuclear localization of NPR1 is required for NPR1's function in plant defense (Tada et al., 2008). Redox changes induced by SA can induce transcriptional reprogramming of jasmonic acid (JA) induced genes by affecting NPR1 and the TGA family of transcription factors (Ndamukong et al., 2007). These redox changes can determine the proteins' sub-cellular localization or DNA binding ability to modify gene expression. Also, SA can cause proteins associated with JA signaling, like ORA59, to be degraded (Van der Does et al., 2013), and can induce negative regulators of JA signaling, specifically WRKY70 and WRKY33 (Li et al., 2004; Zheng et al., 2006). This cross-talk between SA and JA is important to plant defense, because SA-mediated defense is generally more effective against hemi- and biotrophic pathogens, while JA-mediated defense allowing is effective against herbivory and necrotrophic pathogens, the plant to mount a quick, targeted defense against any type of pathogen (Pieterse et al., 2012).

Several proteins assist in the homeostasis of NPR1. Recent research suggests that NPR1 is S-nitrosylated at cysteine-156 by S-nitrosoglutathione (GSNO), which facilitates its oligomerization. In addition, NPR1's monomerization is facilitated by several thioredoxins (TRXs). These reactions regulate NPR1 by sequestering it in the cytosol, or conversely, allowing the free monomer to enter the nucleus

(See Fig. 1) (Tada et al., 2008).

Sumoylation is another method by which the plant cell can post-transcriptionally regulate the function of NPR1. Saleh, et al., discovered that NPR1 is sumoylated after application of SA, dependent on NPR1's phosphorylation. NPR1's sumoylation causes it to switch from interacting with WRKY transcription factors, to interacting with the TGA family of transcription factors that activate transcription of defense-related genes. Sumoylation also causes NPR1 to become degraded, which is essential for its function in fully regulating SA-mediated plant defense (Spoel et al., 2009; Saleh et al., 2015).

Expression of *NPR1* is regulated by a number of WRKY DNA binding proteins. The 5′-UTR of *NPR1* contains two W-box sequences, which are recognized by WRKY proteins that are induced by SA and pathogen infection. These W-boxes are necessary for induction of *NPR1* and activation of SA-mediated plant defense (Yu et al., 2001). Specifically, Chai et al. found that WRKY6 directly binds to the *NPR1* promoter, and that the level of *NPR1* mRNA is reduced in *wrky6* mutants (Chai et al., 2014). Further, they demonstrated that MPK6 works upstream WRKY6, and that SA-induced activation of MPK6 leads to higher expression of WRKY6, ultimately increasing the level of *NPR1* mRNA (Chai et al., 2014).

TGA defense signaling pathway

TGA transcription factors are found in all eukaryotes, and belong to the group of basic region/leucine zipper (bZIP) transcription factors. These transcription factors have a basic region that binds DNA, and a leucine zipper dimerization motif. TGA transcription factors can bind specifically to the canonical sequence TGACGTCA (Jakoby et al., 2002). TGA Transcription factors mediate SAR and *PR* gene expression (Fan and Dong, 2002). NPR1 interacts with TGA transcription factors in the nucleus, stimulating their ability to bind to SA-responsive genetic elements. Functional NPR1 is required for TGA transcription factors to bind to these elements (Després et al., 2000).

There are ten TGA transcription factors, which have been confirmed in *Arabidopsis* (Jakoby et al., 2002). Of those ten, TGA1-TGA7 have been found to interact with NPR1. Those seven TGA transcription factors could be further divided into three classes based on their sequence homology: TGA1 and TGA4; TGA2, TGA5, and TGA6; and TGA3 and TGA7 (Xiang et al., 1997). TGA2/3/5/6/7 have consistent interaction with NPR1 in yeast, and can be transiently expressed *in planta*; however, in SA-induced leaves, TGA1 can bind NPR1, while no interaction was found in yeast. Later, it was confirmed that reduction of two Cys residues in TGA1 determined this SA-dependent interaction (Després et al., 2003). Contrary to previous negative results, Tada, et al., found that NPR1 and TGA4 indeed interact using a GAL4-based yeast system (Tada et al., 2008). Després et al. confirmed that TGA4 weakly interacts with NPR1 using co-immunoprecipation and western blotting techniques *in vitro* (Després et al., 2000). The latest studies show that *PR* gene expression did not change significantly when TGA4 and TGA7 were individually disrupted. There is conflicting evidence regarding TGA2. Pontier et al. reported that TGA2 can enhance *PR-1* expression and SAR (Pontier et al., 2001). TGA5 has been reported to enhance defense against the oomycete parasite, *Peronospora parasitica*, independent of interaction with NPR1 and SA (Kim and Delaney, 2002).

PR genes and their antimicrobial effects

Upon pathogen infection, a group of plant defense genes, called *Pathogenesis-Related* (*PR*) genes, which encode low molecular proteins with antimicrobial activities, are significantly induced (Carr et al., 1989). The *PR1* family in *Arabidopsis* is composed of 22 genes, only one of which is upregulated in response to pathogen infection (van Loon et al., 2006). Interestingly, in rice, which possesses 12 *PR1* genes, all 12 were induced in response to infection with rice blast fungal pathogen, *Magnaporthe grisea* (Mitsuhara et al., 2008). In tobacco, *PR-1a* encodes an acidic secreted protein that was found to bind to ergosterols in fungal membranes, causing cellular leakage. The PR-1a ortholog, *P14c,* in tomato encodes a basic protein, which is stored in the vacuole. These proteins share similar indiscriminate sterol binding capability; however, P14c presumably is released from the vacuole after the cell is lysed in order to flood the pathogen invader and damage its plasma membrane before its sterol biosynthesis mechanisms can adjust (Gamir et al., 2016). The PR-2 family of proteins have β-1,3-glucanase activity in Xanthi-nc (NN) tobacco (Kauffmann et al., 1987), and PR-3 proteins are putative chitinases (Legrand et al., 1987).

Among PRs, *PR-1, PR-2*, and *PR-5* have SA-dependent expression in *Arabidopsis*, and are required for defense against the biotrophic fungus *Peronospora parasitica* (Curto et al., 2006). van Verk et al. (2011), identified a novel tobacco WRKY transcription factor (NtWRKY12) that can bind the promoter of *PR-1a*, which is induced by SA. Several classes of PR proteins, including PR−3, −4, −8, and −11, are believed to be different types of chitinases, conferring resistance to fungal pathogens (Kasprzewska, 2003). Transgenic tomato plants overexpressing either a class I tobacco β-1,3-glucanase or a class I chitinase show no increased resistance to pathogen infection; however, transgenic tomato seed endosperm tissue overexpressing both the β-1,3-glucanase and chitinase shows significant resistance to pathogen infections, indicating a synergistic effect (Wu et al., 2001).

ER transport genes required for defense and SAR

Recent evidence indicates that endoplasmic reticulum (ER) genes, involved in the protein secretion pathway, are also

involved in SA-mediated defense, and are required for systemic acquired resistance (Wang et al., 2005). These secretion-related genes include those encoding the Sec61 translocon complex, a protein complex that allows proteins to cross the ER membrane, and a signal recognition particle receptor, which can recognize proteins with the ER transport signal, then direct them to the translocon complex. It has been reported that the production and secretion of defense proteins depend on the functions of the ER, whose secretory functions can be altered in the presence of SA (Trombetta and Parodi, 2003; Vitale and Denecke, 1999). Many genes encoding ER-resident chaperones and co-chaperones are also induced by NPR1, such as *BiP2, GRP94, DAD1, CNXs, CRTs,* and *PDI*s. The chaperone proteins encoded by these genes are crucial for determining protein co-translational folding and modification in various organelles (Fu and Kreibich, 2000; Wang et al., 2005).

NAD(P) and its role in SA-related defense gene expression

In mammalian tissues, NAD(P) is released into the extracellular compartment during stress, where it activates transmembrane signaling, likely through purinoreceptors (Billington et al., 2006). Zhang and Mou hypothesized that the same may be true of plant tissues during pathogen attack. After infiltrating leaf tissues with $NADP^+$, they found that expression of *PR1, PR2,* and *PR5* could be induced in a dose-dependent manner. Similarly, they also infiltrated $NADP^+$, NAD^+, and ATP, but observed no induction of *PR* gene expression when using ATP, and a similar induction when using $NADP^+$ and NAD^+. This indicates that the induction does not depend on the oxidation state of $NADP^+$, and that the induction depends on receptors for pyridine nucleotides. Additionally, treatment with these pyridine nucleotides causes SA to accumulate in treated tissues and enhanced resistance to *Psm* ES4326; however, there is a difference in induction capabilities between NAD^+ and $NADP^+$. It seems that $NADP^+$ can only partially induce resistance in *sid2* and *npr1* mutants, while NAD^+ can fully restore resistance against bacterial pathogens in these mutants (Zhang and Mou, 2009). These data demonstrate the importance of the presence and perception of extracellular molecules in SA-mediated plant defense signaling.

After screening for mutants that were insensitive to extracellular NAD, An, et al., identified *ien2,* which has a mutation in the gene encoding ELONGATA3 (ELO3), an Elongator complex subunit. Elongator subunit mutations result in diverse phenotypes including: resistance to oxidative stress, abnormal root development, increased pathogen susceptibility, severe auxin phenotypes, and sensitivity to abscisic acid. ELO3 has been shown to be responsible for the rapid induction of transcriptional reprogramming in response to *Pst* DC3000, acting as an epigenetic regulator of defense genes (An et al., 2016).

WRKY transcription factors involved in plant defense signaling

WRKY proteins are defined as a class of DNA binding proteins, which possess a conserved N-terminal amino acid sequence, WRKYGQK, and a novel C-terminal zinc finger motif. WRKY proteins recognize TTGAC(C/T) W-box elements, which are often located in the promoters of plant defense-related genes, such as the *PR* genes (Dong et al., 2003). Most of the analyzed WRKY genes are capable of responding to pathogen defense and are involved in defense signaling (Eulgem and Somssich, 2007). Several WRKY protein-regulated genes were found to be induced after application of SA in *Arabidopsis* (Dong et al., 2003). SA-induced WRKY proteins also regulate the expression of NPR1 and other regulatory proteins (Yu et al., 2001). The *Arabidopsis* WRKY family contains 74 genes, while the rice WRKY family has more than 90 members (Eulgem et al., 2000). Phylogenetic analysis demonstrated that the functions of WRKY proteins are conserved in monocots and dicots (Mangelsen et al., 2008). Many reports demonstrate that WRKY transcription factors are involved in disease resistance. For example, overexpression of *WRKY18* causes increased resistance against two bacterial pathogens in plants (Chen C. and Chen Z., 2002). Plants overexpressing *WRKY70* exhibited strengthened SA-mediated resistance with impaired resistance mediated by jasmonic acid (Li et al., 2004). WRKY53 is involved in leaf senescence (Miao et al., 2004). Among 64 genes, WRKY18/38/53/54/58/59/66/70 were identified as direct transcriptional targets of NPR1. WRKY18 showed positive regulation for full induction of SAR, while WRKY58 negatively regulated SAR (Wang et al., 2006).

Additional SA receptors and SA binding proteins

In *N. benthamiana,* three SA binding proteins (SABPs) have been isolated. SABP1 was found to be a catalase enzyme, possibly involved in the HR response in local tissue. SABP2 was shown to be an SA-stimulated lipase (Delaney, 2005). SABP3 has been identified as a chloroplast carbonic anhydrase, which exhibits both enzymatic and SA binding activities (Slaymaker et al., 2002). Current research estimates that there are 30 SABP's, most of which play a role in plant immunity (Tian et al., 2012).

NPR3 and NPR4 both bind SA, and serve to modulate SA-mediated plant defense in the presence of jasmonic acid (JA). During ETI, both SA and JA are induced to high levels. JA, which is normally associated with defense against necrotrophic pathogens, is induced during ETI in order to protect against simultaneous attack by biotrophic and necrotrophic pathogens in areas where programmed cell death has occurred. In fact, this phenomenon explains why plant tissue adjacent to areas of programmed cell death are not susceptible

to necrotrophic pathogen infection (Spoel et al., 2007). Liu, et al., recently discovered that NPR3 and NPR4 mediate concurrent induction of SA and JA by causing degradation of the JAZ proteins, which repress transcription of JA-responsive genes. This represents a non-canonical activation of the JA signaling pathway, through SA receptors NPR3 and NPR4, rather than through activation of JA receptor COI1 (CORONATINE INSENSITIVE 1) (Liu et al., 2016).

Choi et al. recently discovered that High Mobility Group Box 3 (HMGB3) binds SA. HMGB3 is a Damage-Associated Molecular Pattern (DAMP) that plays a role in regulating MT2, including inducing defense related genes, increasing callose deposition, and enhancing pathogen resistance. HMGB3 is released into the apoplast following infection by a necrotrophic pathogen such as *B. cinerea*. After its release, HMGB3 interacts with an unknown LRR-RLK PRR associated with BAK1 and BKK1, similarly to MAMPs. In the apoplast, HMGB3 binds SA, and its DAMP activity is reduced. This indicates that the jasmonic acid and ethylene pathways, which are associated with defense against necrotrophic pathogens, and the SA-mediated defense pathway are intertwined. HMGB3's effect against hemi- and biotrophic pathogens is negligible, and the presence of SA seems to be responsible for this (Choi et al., 2016).

Connection between MTI and SA-mediated plant immunity

Plant biologists studying plant defense have sought to discover the link between ETI and MTI, but it seems that Kong, et al., have made one step closer to discovering the link. Pattern-Triggered Immunity Compromised Receptor-like Cytoplasmic Kinase1 (PCRK1) and PCRK2 are kinases that are known to interact with the PRR FLS2. These researchers identified a *pcrk1 pcrk2* double mutant that was deficient in SA-mediated plant defense. The double mutant can only accumulate about half the amount of SA compared with WT after pathogen inoculation. They discovered that PCRK1/2 are rapidly phosphorylated after the plant is exposed to the synthetic flg22 peptide, and act downstream on two transcription factors, SARD1 and CBP60g, both of which induce expression of *ICS1*, thereby influencing SA mediated plant defense by altering SA biosynthesis (Kong et al., 2016).

Research suggests that application of SA can prime plant defense upon detection of flg22, the synthetic flagellin epitope. Yi and Kwoon measured the flg22-triggered oxidative burst in Col-0, *sid2,* and *eds5 Arabidopsis.* They found that the oxidative burst was suppressed in the *sid2* and *eds5* mutants. To confirm their results, they measured the induction of *WRKY29* and *FRK1* using RT-qPCR, and found that the induction of these defense-related genes was reduced by 50% in the *sid2* mutant. After pre-treatment with SA, they discovered that in addition to amplifying the flg22-triggered oxidative burst in Col-0 *Arabidopsis*, SA increased the level of *FLS2* mRNA (Yi and Kwon, 2014).

Circadian clock-related genes and SA-mediated plant defense

The circadian clock is a highly conserved system of proteins that coordinate the physiology and behavior of living things with daily environmental change, regulating plant growth and development (Edgar et al., 2012). The core components of the circadian clock, a central self-sustaining oscillator with a period of about 24 h, consist of various negative feedback loops, which are related to each other in *Arabidopsis* (McClung, 2008; Harmer, 2009). Those loops are responsible for responding to external stimuli individually. Among clock components, CIRCADIAN CLOCK ASSOCIATED1 (CCA1) and its homolog LATE ELONGATED HYPOCOTYL (LHY) are grouped into transcription factor families, which are responsible for multiple feedback loops and orchestrate clock activity (Alabadí et al., 2002; Mizoguchi et al., 2002; Lu et al., 2009; Wang et al., 2011b). Recently, crosstalk between the circadian clock and plant innate immunity has been revealed. CCA1 and LHY co-regulate basal and resistance gene-mediated defense against *Pseudomonas syringae* and *Hyaloperonospora arabidopsidis* (Wei et al., 2011). In overexpresssion mutants of CCA1 and LHY, *Arabidopsis* showed severely increased susceptibility to *P. syringae*. GRP7, a downstream target of CCA1 and LHY, is regulated by the circadian clock and demonstrated to affect plant defense and stomatal activity (Zhang et al., 2013).

NPR1 has also been found to be involved in regulating the circadian clock genes. By regulating the expression *of TIMING OF CAB2 EXPRESSION 1 (TOC1), LHY,* and *CCA1*, but not changing their phase, NPR1 can reinforce the circadian clock. It is thought that the reinforcement of the circadian clock enables the plant to increase photosynthesis and gate the immune response to the morning, while preserving the ability to grow for night (Zhou et al., 2015).

PHOSPHATE TRANSPORTER 4;1 (PHT4;1) is another protein regulated by the circadian clock. The dominant *pht4;1-1* mutant is more susceptible to several virulent *Pseudomonas syringae* strains. This susceptibility can be suppressed by treating the mutant with SA, indicating that PHT4;1 is upstream of SA signaling. *PHT4;1* possesses two CCA1 binding sites in its promotor, and its RNA transcript is degraded in the dark, which indicates that PHT4;1 is under control of the circadian clock, and that light is required for its expression (Wang et al., 2011a).

SA-primed viral gene silencing

SA induces genes involved in gene silencing to suppress viral pathogens. Researchers studying the plum pox virus (PPV) discovered that *Nicotiana tabacum* plants expressing *NahG*, salicylate hydroxylase, developed systemic PPV infections (Alamillo et al., 2006). This pathogen normally cannot spread

systemically in this host, although it can cause local cell death at its point of entry. They also showed that accumulation of PPV in infected tissues was higher in plants that were deficient in SA. In addition, the *NahG* plants showed reduced viral derived small RNAs. Taken together, this research indicates that a SA-mediated defense mechanism and a RNA-silencing mechanism work together to limit the spread of this virus (Alamillo et al., 2006). In tomato, several RNA silencing genes are induced after ToMV and CEVd viral infection: *Arabidopsis* orthologs *ToDCL1, ToDCL2, ToDCL4,* and *ToRDR1*. In their study, Campos, et al. found *ToDCL1, ToDCL2, ToRDR1, and ToRDR2* are significantly induced after SA treatment, resulting in a delay in accumulation of pathogenic RNA in inoculated plants. This indicates that SA has the ability to prime defense by pre-inducing RNA silencing genes (Campos et al., 2014).

Cmv2b is a viral protein produced by the *Cucumber mosaic* virus that is required for systemic viral infection in cucumber plants, and is found to be involved in suppressing RNA silencing in tobacco. Ji et al. discovered that by deleting *Cmv2b*, the systemic spread of the virus could be halted in older *N. glutinosa* plants, with very mild symptoms, and reduced viral accumulation appearing in younger plants. When they pre-treated their tobacco plants with SA, they observed a reduction of CMV RNAs in systemic leaves by up to 7-fold (Ji and Ding, 2001). *ALTERNATIVE OXIDASE* (*Aox)* is a gene involved in SA-mediated virus resistance that is rapidly induced by SA. Its induction is suppressed in systemic leaves after infection with WT CMV, but not CMV lacking the Cmv2b protein (Ji and Ding, 2001). This research seems to indicate that viral proteins target SA-mediated viral resistance by blocking induction of SA-induced defense genes.

Another recent study using *Tomato Ringspot Virus* (ToRSV) revealed that SA treatment can reduce the size of viral lesions found on infected tobacco leaves, and that this reduction is abolished in *NahG* expressing plants. They also found that, because SA can induce RDR1, SA treatment can restrict the systemic spread of the virus. This data indicates that SA is critical to the induction of antiviral plant defenses, which include RNA silencing, HR, and a moderate form of SAR (Jovel et al., 2011).

Regulation of autophagy by SA and NPR1

Autophagy is a degradation process, which delivers cytoplasmic ingredients to the vacuole or lysosome. The molecular mechanism for autophagy has been well studied and 18 autophagy-related (ATG) genes for autophagosome formation are identified in yeast (*Saccharomyces cerevisiae*). *Arabidopsis* possesses 30 autophagy-related genes, which correspond to 14 yeast *ATG* genes. Four out of 30 *AtATG* genes have not been characterized (Hanaoka et al., 2002). The remaining genes are found to be highly conserved in plant and animal kingdoms. In addition, autophagy activity is lost in *Arabidopsis* ATG-deficient mutants, indicating that ATG genes encode proteins for plant autophagy. In *atg* mutants, accelerated programmed cell death in senescence and immunity were found to be SA signaling dependent. When treatment of SA is performed, senescence and cell death occur in SA-deficient *atg* mutants; however, *atg npr1* plants show normal growth. This research suggests that the early senescence phenotype is caused by an over-accumulation of ubiquitinated defense protein aggregates, causing stress to the ER, and disruption of cellular homeostasis. This disruption leads to the accumulation of SA, causing the over-accumulation of defense-related transcripts, which is NPR1-dependent. This phenomenon confirms that the cell death in *atg* mutants is dependent on NPR1 (Munch et al., 2014).

Missing links in current research

Although scientists are learning more about how NPR1 regulates salicylic acid-mediated plant defense, much is still unknown. The point of cross-talk between MTI and ETI remains elusive (Tully et al., 2014). Current research suggests that NPR1 plays a role in MTI. Plants treated with low levels of SA exhibited an enhanced level of MAPK3 and MAPK6 activation when exposed to flg22, indicating that NPR1 is involved in the MTI pathway, and is required for an enhanced response to flg22 (Yi et al., 2015), but the feedback regulator of FLS2, which senses bacterial flagellin and the synthetic epitope flg22, is unknown. The precise role of effectors targeting proteins involved in SA biosynthesis or SA receptors remains largely unknown. Current research suggests that NPR1 and SA are involved in regulating programmed cell death during immune responses and senescence, but the mechanism of this regulation is unknown (Yoshimoto et al., 2009) .

Interestingly, the necrotrophic pathogen, *Botrytis cinerea,* fails to induce SAR (Govrin and Levine, 2002). This pathogen is non-specific, infecting over 200 species of plants, including many crops (Prins et al., 2000). Additional research is needed to understand how *B. cinerea* can infect the plant without inducing SAR, and why prior inoculation with *P. syringea* to induce SAR does not suppress lesion formation nor growth of *B. cinerea* (Govrin and Levine, 2002).

The role of SA in roots against soil-borne pathogens also remains elusive, but current research suggests that SA produced by non-pathogenic rhizobacteria aids in disease resistance. In a study of *Pseudomonas aeruginosa* 7NSK2, it was found that the SA produced by this bacterium was necessary to induce resistance to the previously mentioned necrotrophic bacterium *Botrytis cinerea* in bean (De Meyer, 1997).

Future research into NPR1's role in SA-mediated plant defense may progress further down many avenues. One prospective avenue is the investigation of heterotrimeric G-proteins and their role in regulating plant defense. Hetero-

trimeric G-proteins have been found to interact with many different proteins in many different biological processes, including regulating cell wall modification and saline stress in plants (Klopffleisch et al., 2011; Colaneri et al., 2014). G-proteins have also been implicated in transducing transmembrane signals from receptor-like kinases (Ishikawa, 2009; Liu et al.,2013). G-protein mutants show impaired resistance to various pathogenic microbes, and reduced sensitivity to various exogenous MAMPs (Maeda et al., 2009; Zeng and He, 2010; Lee et al., 2013; Liu et al., 2013; Lorek et al., 2013; Torres et al., 2013). Further research is required to discover if NPR1 also plays a role in G-protein MAMP signaling or if these G-proteins are involved in SA-mediated plant defense.

Acknowledgements

This work is financially supported by NSF EAGER grant 1464527 (Z.F.).

Compliance with ethics guideline

Ian Palmer, Zhenhua Shang, and Zhengqing Fu declare no conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

Agriculture, U.S.D.o. and N.A.S. Service (2015). Citrus Fruits 2015 Summary (September 2015)

Alabadí D, Yanovsky M J, Más P, Harmer S L, Kay S A (2002). Critical role for CCA1 and LHY in maintaining circadian rhythmicity in Arabidopsis. Curr Biol, 12(9): 757–761

Alamillo J M, Saénz P, García J A (2006). Salicylic acid-mediated and RNA-silencing defense mechanisms cooperate in the restriction of systemic spread of plum pox virus in tobacco. Plant J, 48(2): 217–227

An C, Ding Y, Zhang X, Wang C, Mou Z (2016). Elongator plays a positive role in exogenous NAD-induced defense responses in *Arabidopsis*. Mol Plant Microbe Interact, 29(5): 396–404

An C, Mou Z (2011). Salicylic acid and its function in plant immunity. J Integr Plant Biol, 53(6): 412–428

Anand A, Uppalapati S R, Ryu C M, Allen S N, Kang L, Tang Y, Mysore K S (2008). Salicylic acid and systemic acquired resistance play a role in attenuating crown gall disease caused by Agrobacterium tumefaciens. Plant Physiol, 146(2): 703–715

Attaran E, Zeier T E, Griebel T, Zeier J (2009). Methyl salicylate production and jasmonate signaling are not essential for systemic acquired resistance in *Arabidopsis*. Plant Cell, 21(3): 954–971

Axtell M J, McNellis T W, Mudgett M B, Hsu C S, Staskawicz B J (2001). Mutational analysis of the *Arabidopsis* RPS2 disease resistance gene and the corresponding pseudomonas syringae avrRpt2 avirulence gene. Mol Plant Microbe Interact, 14(2): 181–188

Bhattacharjee S, Halane M K, Kim S H, Gassmann W (2011). Pathogen effectors target *Arabidopsis* EDS1 and alter its interactions with immune regulators. Science, 334(6061): 1405–1408

Billington R A, Bruzzone S, De Flora A, Genazzani A A, Koch-Nolte F, Ziegler M, Zocchi E(2006). Emerging functions of extracellular pyridine nucleotides. Mol Med, 12(11-12): 324–327

Boller T, Felix G (2009). A renaissance of elicitors: perception of microbe-associated molecular patterns and danger signals by pattern-recognition receptors. Annu Rev Plant Biol, 60(1): 379–406

Cameron R, Zaton K (2004). Intercellular salicylic acid accumulation is important for age-related resistance in *Arabidopsis to Pseudomonas syringae*. Physiol Mol Plant Pathol, 65(4): 197–209

Campos L, Granell P, Tárraga S, López-Gresa P, Conejero V, Bellés J M, Rodrigo I, Lisón P (2014). Salicylic acid and gentisic acid induce RNA silencing-related genes and plant resistance to RNA pathogens. Plant Physiol Biochem, 77: 35–43

Carr J P, Beachy R N, Klessig D F (1989). Are the PR1 proteins of tobacco involved in genetically engineered resistance to TMV? Virology, 169(2): 470–473

Carviel J L, Al-Daoud F, Neumann M, Mohammad A, Provart N J, Moeder W, Yoshioka K, Cameron R K (2009). Forward and reverse genetics to identify genes involved in the age-related resistance response in *Arabidopsis thaliana*. Mol Plant Pathol, 10(5): 621–634

Carviel J L, Wilson D C, Isaacs M, Carella P, Catana V, Golding B, Weretilnyk E A, Cameron R K (2014). Investigation of intercellular salicylic acid accumulation during compatible and incompatible *Arabidopsis-Pseudomonas syringae* interactions using a fast neutron-generated mutant allele of EDS5 identified by genetic mapping and whole-genome sequencing. PLoS One, 9(3): e88608

Chai J, Liu J, Zhou J, Xing D (2014). Mitogen-activated protein kinase 6 regulates NPR1 gene expression and activation during leaf senescence induced by salicylic acid. J Exp Bot, 65(22): 6513–6528

Chen C, Chen Z (2002). Potentiation of developmentally regulated plant defense response by AtWRKY18, a pathogen-induced *Arabidopsis* transcription factor. Plant Physiol, 129(2): 706–716

Chen F, D'Auria J C, Tholl D, Ross J R, Gershenzon J, Noel J P, Pichersky E (2003). An *Arabidopsis thaliana* gene for methylsalicylate biosynthesis, identified by a biochemical genomics approach, has a role in defense. Plant J, 36(5): 577–588

Cheng W, Munkvold K R, Gao H, Mathieu J, Schwizer S, Wang S, Yan Y B, Wang J, Martin G B, Chai J (2011). Structural analysis of *Pseudomonas syringae* AvrPtoB bound to host BAK1 reveals two similar kinase-interacting domains in a type III Effector. Cell Host Microbe, 10(6): 616–626

Choi H W, Manohar M, Manosalva P, Tian M, Moreau M, Klessig D F (2016). Activation of plant innate immunity by extracellular high mobility group Box 3 and its inhibition by salicylic acid. PLoS Pathog, 12(3): e1005518

Colaneri A C, Tunc-Ozdemir M, Huang J P, Jones A M (2014). Growth attenuation under saline stress is mediated by the heterotrimeric G protein complex. BMC Plant Biol, 14(1): 129–139

Curto M, Camafeita E, Lopez J A, Maldonado A M, Rubiales D, Jorrín J V (2006). A proteomic approach to study pea (*Pisum sativum*) responses to powdery mildew (*Erysiphe pisi*). Proteomics, 6(S1 Suppl 1): S163–S174

De Meyer G H M (1997). Salicylic acid produced by the *Rhizobacterium Pseudomonas aeruginosa* 7NSK2 induces resistance to leaf infection

by *Botrytis cinerea* on bean., Gent, Belgium: Phytopathology.

Dean J V, Mohammed L A, Fitzpatrick T (2005). The formation, vacuolar localization, and tonoplast transport of salicylic acid glucose conjugates in tobacco cell suspension cultures. Planta, 221(2): 287–296

Dean J V M, Mills J D (2004). Uptake of salicylic acid 2-O-beta-D-glucose into soybean tonoplast vesicles by an ATP-binding cassette transporter-type mechanism. Physiol Plant, 120(4): 603–612

Delaney T P (2005). Salicylic Acid. In: Davies P J (Ed.), Plant Hormones: Biosynthesis, Signal Tranduction, Action!, Kluwer Academic Publishers, Dordrecht, The Netherlands. pp. 635–653

Delaney T P, Uknes S, Vernooij B, Friedrich L, Weymann K, Negrotto D, Gaffney T, Gut-Rella M, Kessmann H, Ward E, Ryals J (1994). A central role of salicylic acid in plant disease resistance. Science, 266 (5188): 1247–1250

Després C, Chubak C, Rochon A, Clark R, Bethune T, Desveaux D, Fobert P R (2003). The *Arabidopsis* NPR1 disease resistance protein is a novel cofactor that confers redox regulation of DNA binding activity to the basic domain/leucine zipper transcription factor TGA1. Plant Cell, 15(9): 2181–2191

Després C, DeLong C, Glaze S, Liu E, Fobert P R (2000). The *Arabidopsis* NPR1/NIM1 protein enhances the DNA binding activity of a subgroup of the TGA family of bZIP transcription factors. Plant Cell, 12(2): 279–290

DeWitt D L, el-Harith E A, Kraemer S A, Andrews M J, Yao E F, Armstrong R L, Smith W L (1990). The aspirin and heme-binding sites of ovine and murine prostaglandin endoperoxide synthases. J Biol Chem, 265(9): 5192–5198

Ding Y, Dommel M, Mou Z (2016). Abscisic acid promotes proteasome-mediated degradation of the transcription coactivator NPR1 in *Arabidopsis* thaliana. Plant J, 86(1): 20–34

Dong J, Chen C, Chen Z (2003). Expression profiles of the *Arabidopsis* WRKY gene superfamily during plant defense response. Plant Mol Biol, 51(1): 21–37

Durrant W E, Dong X (2004). Systemic acquired resistance. Annu Rev Phytopathol, 42(1): 185–209

Edgar R S, Green E W, Zhao Y, van Ooijen G, Olmedo M, Qin X, Xu Y, Pan M, Valekunja U K, Feeney K A, Maywood E S, Hastings M H, Baliga N S, Merrow M, Millar A J, Johnson C H, Kyriacou C P, O'Neill J S, Reddy A B (2012). Peroxiredoxins are conserved markers of circadian rhythms. Nature, 485(7399): 459–464

Eulgem T, Rushton P J, Robatzek S, Somssich I E (2000). The WRKY superfamily of plant transcription factors. Trends Plant Sci, 5(5): 199–206

Eulgem T, Somssich I E (2007). Networks of WRKY transcription factors in defense signaling. Curr Opin Plant Biol, 10(4): 366–371

Falk A, Feys B J, Frost L N, Jones J D, Daniels M J, Parker J E(1999). EDS1, an essential component of R gene-mediated disease resistance in *Arabidopsis* has homology to eukaryotic lipases. Proc Natl Acad Sci USA, 96(6): 3292–3297

Fan W, Dong X (2002). In vivo interaction between NPR1 and transcription factor TGA2 leads to salicylic acid-mediated gene activation in *Arabidopsis*. Plant Cell, 14(6): 1377–1389

Feys B J, Moisan L J, Newman M A, Parker J E (2001). Direct interaction between the *Arabidopsis* disease resistance signaling proteins, EDS1 and PAD4. EMBO J, 20(19): 5400–5411

Feys B J,Wiermer M, Bhat R A, Moisan L J, Medina-Escobar N, Neu C, Cabral A, Parker J E (2005). *Arabidopsis* SENESCENCE-ASSOCIATED GENE101 stabilizes and signals within an ENHANCED DISEASE SUSCEPTIBILITY1 complex in plant innate immunity. Plant Cell, 17(9): 2601–2613

Fragnière C, Serrano M, Abou-Mansour E, Métraux J P, L'Haridon F (2011). Salicylic acid and its location in response to biotic and abiotic stress. FEBS Lett, 585(12): 1847–1852

Fu J, Kreibich G (2000). Retention of subunits of the oligosaccharyl-transferase complex in the endoplasmic reticulum. J Biol Chem, 275 (6): 3984–3990

Fu Z Q, Dong X (2013). Systemic acquired resistance: turning local infection into global defense. Annu Rev Plant Biol, 64(1): 839–863

Gamir J, Darwiche R, Van't Hof P, Choudhary V, Stumpe M, Schneiter R, Mauch F(2017). The sterol-binding activity of PATHOGENESIS-RELATED PROTEIN 1 reveals the mode of action of an antimicrobial protein. The Plant Journal, 89(3):502–509

Glazebrook J (2005). Contrasting mechanisms of defense against biotrophic and necrotrophic pathogens. Annu Rev Phytopathol, 43 (1): 205–227

Goldfine A B, Fonseca V, Jablonski K A, Chen Y D, Tipton L, Staten M A, Shoelson S E, and the Targeting Inflammation Using Salsalate in Type 2 Diabetes Study Team (2013). Salicylate (salsalate) in patients with type 2 diabetes: a randomized trial. Ann Intern Med, 159(1): 1–12

Govrin E M L, Levine A (2002). Infection of *Arabidopsis* with a necrotrophic pathogen, Botrytis cinerea, elicits various defense responses but does not induce systemic acquired resistance (SAR). Plant Mol Biol, 48(3): 267–276

Gráda Ó C(2007). Ireland's Great Famine. Dublin: University College Dublin Press

Hanaoka H, Noda T, Shirano Y, Kato T, Hayashi H, Shibata D, Tabata S, Ohsumi Y (2002). Leaf senescence and starvation-induced chlorosis are accelerated by the disruption of an *Arabidopsis* autophagy gene. Plant Physiol, 129(3): 1181–1193

Harmer S L(2009). The circadian system in higher plants. Annu Rev Plant Biol, 60(1): 357–377

Hawley S A, Fullerton M D, Ross F A, Schertzer J D, Chevtzoff C, Walker K J, Peggie M W, Zibrova D, Green K A, Mustard K J, Kemp B E, Sakamoto K, Steinberg G R, Hardie D G (2012). The ancient drug salicylate directly activates AMP-activated protein kinase. Science, 336(6083): 918–922

Heidrich K, Wirthmueller L, Tasset C, Pouzet C, Deslandes L, Parker J E (2011). Arabidopsis EDS1 connects pathogen effector recognition to cell compartment-specific immune responses. Science, 334(6061): 1401–1404

Huang J, Gu M, Lai Z, Fan B, Shi K, Zhou Y H, Yu J Q, Chen Z (2010). Functional analysis of the *Arabidopsis* PAL gene family in plant growth, development, and response to environmental stress. Plant Physiol, 153(4): 1526–1538

Ishikawa A (2009). The *Arabidopsis* G-protein -subunit is required for defense response against *Agrobacterium tumefaciens*. Biosci Biotechnol Biochem, 73(1): 47–52

Jakoby M, Weisshaar B, Dröge-Laser W, Vicente-Carbajosa J,

Tiedemann J, Kroj T, Parcy F, and the bZIP Research Group (2002). bZIP transcription factors in *Arabidopsis*. Trends Plant Sci, 7(3): 106–111

Jelenska J, Yao N, Vinatzer B A, Wright C M, Brodsky J L, Greenberg J T (2007). A J domain virulence effector of *Pseudomonas syringae* remodels host chloroplasts and suppresses defenses. Curr Biol, 17(6): 499–508

Ji L H, Ding S W (2001). The suppressor of transgene RNA silencing encoded by Cucumber mosaic virus interferes with salicylic acid-mediated virus resistance. Mol Plant Microbe Interact, 14(6): 715–724

Jirage D, Tootle T L, Reuber T L, Frost L N, Feys B J, Parker J E, Ausubel F M, Glazebrook J (1999). *Arabidopsis thaliana* PAD4 encodes a lipase-like gene that is important for salicylic acid signaling. Proc Natl Acad Sci USA, 96(23): 13583–13588

Jovel J, Walker M, Sanfaçon H (2011). Salicylic acid-dependent restriction of Tomato ringspot virus spread in tobacco is accompanied by a hypersensitive response, local RNA silencing, and moderate systemic resistance. Mol Plant Microbe Interact, 24(6): 706–718

Kasprzewska A (2003). Plant chitinases–regulation and function. Cell Mol Biol Lett, 8(3): 809–824

Kauffmann S, Legrand M, Geoffroy P, Fritig B (1987). Biological function of; pathogenesis-related' proteins: four PR proteins of tobacco have 1,3-β-glucanase activity. EMBO J, 6(11): 3209–3212

Kim H S, Delaney T P (2002). Over-expression of TGA5, which encodes a bZIP transcription factor that interacts with NIM1/NPR1, confers SAR-independent resistance in *Arabidopsis thaliana* to *Peronospora parasitica*. Plant J, 32(2): 151–163

Kim S H, Kwon S I, Bhattacharjee S, Gassmann W (2009). Regulation of defense gene expression by *Arabidopsis* SRFR1. Plant Signal Behav, 4(2): 149–150

Klopffleisch K, Phan N, Augustin K, Bayne R S, Booker K S, Botella J R, Carpita N C, Carr T, Chen J G, Cooke T R, Frick-Cheng A, Friedman E J, Fulk B, Hahn M G, Jiang K, Jorda L, Kruppe L, Liu C, Lorek J, McCann M C, Molina A, Moriyama E N, Mukhtar M S, Mudgil Y, Pattathil S, Schwarz J, Seta S, Tan M, Temp U, Trusov Y, Urano D, Welter B, Yang J, Panstruga R, Uhrig J F, Jones A M (2011). *Arabidopsis* G-protein interactome reveals connections to cell wall carbohydrates and morphogenesis. Mol Syst Biol, 7(1): 532

Kong Q, Sun T, Qu N, Ma J, Li M, Cheng Y T, Zhang Q, Wu D, Zhang Z, Zhang Y (2016). Two redundant receptor-like cytoplasmic kinases function downstream of pattern recognition receptors to regulate activation of SA biosynthesis. Plant Physiol, 171(2): 1344–1354

Kopp E, Ghosh S (1994). Inhibition of NF-kappa B by sodium salicylate and aspirin. Science, 265(5174): 956–959

Kunta M, Sétamou M, Skaria M, Rascoe J E, Li W, Nakhla M K, da Graça J V (2012). First report of citrus huanglongbing in Texas. Phytopathology, 102: S4

Kwon S I, Kim S H, Bhattacharjee S, Noh J J, Gassmann W (2009). SRFR1, a suppressor of effector-triggered immunity, encodes a conserved tetratricopeptide repeat protein with similarity to transcriptional repressors. Plant J, 57(1): 109–119

Lee S, Rojas C M, Ishiga Y, Pandey S, Mysore K S (2013). *Arabidopsis* heterotrimeric G-proteins play a critical role in host and nonhost resistance against *Pseudomonas syringae* pathogens. PLoS One, 8 (12): e82445

Legrand M, Kauffmann S, Geoffroy P, Fritig B (1987). Biological function of pathogenesis-related proteins: Four tobacco pathogenesis-related proteins are chitinases. Proc Natl Acad Sci USA, 84(19): 6750–6754

Li J, Brader G, Palva E T (2004). The WRKY70 transcription factor: a node of convergence for jasmonate-mediated and salicylate-mediated signals in plant defense. Plant Cell, 16(2): 319–331

Lin K H, Lin K H (1956) *THE CITRUS HUANG LUNG BIN (GREENING) DISEASE IN CHINA*. Acta Phytopathologica Sinica, Vol. II, Part 1, No. I, and Part 2, p. 1–11 and 14–38

Liu J, Ding P, Sun T, Nitta Y, Dong O, Huang X, Yang W, Li X, Botella J R, Zhang Y (2013). Heterotrimeric G proteins serve as a converging point in multiple receptor-like kinases. Plant Physiol, 161(4):: 2146–2158

Liu L, Sonbol F M, Huot B, Gu Y, Withers J, Mwimba M, Yao J, He S Y, Dong X (2016). Salicylic acid receptors activate jasmonic acid signalling through a non-canonical pathway to promote effector-triggered immunity. Nat Commun, 7:13099

Lorek J, Griebel T, Jones A M, Kuhn H, Panstruga R (2013). The role of *Arabidopsis* heterotrimeric G-protein subunits in MLO2 function and MAMP-triggered immunity. Mol Plant Microbe Interact, 26(9): 991–1003

Lu H, Greenberg J T, Holuigue L (2016). Editorial: Salicylic acid signaling networks. Front Plant Sci, 7: 238

Lu S X, Knowles S M, Andronis C, Ong M S, Tobin E M (2009). CIRCADIAN CLOCK ASSOCIATED1 and LATE ELONGATED HYPOCOTYL function synergistically in the circadian clock of Arabidopsis. Plant Physiol, 150(2): 834–843

Mackey D, Belkhadir Y, Alonso J M, Ecker J R, Dangl J L (2003). *Arabidopsis* RIN4 is a target of the type III virulence effector AvrRpt2 and modulates RPS2-mediated resistance. Cell, 112(3): 379–389

Maeda K, Houjyou Y, Komatsu T, Hori H, Kodaira T, Ishikawa A (2009). AGB1 and PMR5 contribute to PEN2-mediated preinvasion resistance to *Magnaporthe oryzae* in *Arabidopsis thaliana*. Mol Plant Microbe Interact, 22(11): 1331–1340

Mangelsen E, Kilian J, Berendzen K W, Kolukisaoglu U H, Harter K, Jansson C, Wanke D (2008). Phylogenetic and comparative gene expression analysis of barley (Hordeum vulgare) WRKY transcription factor family reveals putatively retained functions between monocots and dicots. BMC Genomics, 28(9):194

Mauch-Mani B, Slusarenko A J(1996). Production of salicylic acid precursors is a major function of phenylalanine ammonia-lyase in the resistance of *Arabidopsis* to *Peronospora parasitica*. Plant Cell, 8(2): 203–212

McClung C R (2008). Comes a time. Curr Opin Plant Biol, 11(5): 514–520

Miao Y, Laun T, Zimmermann P, Zentgraf U (2004). Targets of the WRKY53 transcription factor and its role during leaf senescence in Arabidopsis. Plant Mol Biol, 55(6): 853–867

Mitsuhara I, Iwai T, Seo S, Yanagawa Y, Kawahigasi H, Hirose S, Ohkawa Y, Ohashi Y (2008). Characteristic expression of twelve rice PR1 family genes in response to pathogen infection, wounding, and defense-related signal compounds (121/180). Mol Genet Genomics,

279(4): 415–427

Mizoguchi T, Wheatley K, Hanzawa Y, Wright L, Mizoguchi M, Song H R, Carré I A, Coupland G (2002). LHY and CCA1 are partially redundant genes required to maintain circadian rhythms in Arabidopsis. Dev Cell, 2(5): 629–641

Mosher S, Moeder W, Nishimura N, Jikumaru Y, Joo S H, Urquhart W, Klessig D F, Kim S K, Nambara E, Yoshioka K (2010). The lesion-mimic mutant cpr22 shows alterations in abscisic acid signaling and abscisic acid insensitivity in a salicylic acid-dependent manner. Plant Physiol, 152(4): 1901–1913

Mou Z, Fan W, Dong X (2003). Inducers of plant systemic acquired resistance regulate NPR1 function through redox changes. Cell, 113 (7): 935–944

Munch D, Rodriguez E, Bressendorff S, Park O K, Hofius D, Petersen M (2014). Autophagy deficiency leads to accumulation of ubiquitinated proteins, ER stress, and cell death in *Arabidopsis*. Autophagy, 10(9): 1579–1587

Myers R L(2007). The 100 most important chemical compounds: a reference guide. p. 10–12.

Nawrath C, Heck S, Parinthawong N, Métraux J P (2002). EDS5, an essential component of salicylic acid-dependent signaling for disease resistance in *Arabidopsis*, is a member of the MATE transporter family. Plant Cell, 14(1): 275–286

Ndamukong I, Abdallat A A, Thurow C, Fode B, Zander M, Weigel R, Gatz C (2007). SA-inducible *Arabidopsis* glutaredoxin interacts with TGA factors and suppresses JA-responsive PDF1.2 transcription. Plant J, 50(1): 128–139

Nobuta K, Okrent R A, Stoutemyer M, Rodibaugh N, Kempema L, Wildermuth M C, Innes R W (2007). The GH3 acyl adenylase family member PBS3 regulates salicylic acid-dependent defense responses in *Arabidopsis*. Plant Physiol, 144(2): 1144–1156

Pajerowska-Mukhtar K M, Emerine D K, Mukhtar M S (2013). Tell me more: roles of NPRs in plant immunity. Trends Plant Sci, 18(7): 402–411

Parker J E, Holub E B, Frost L N, Falk A, Gunn N D, Daniels M J (1996). Characterization of eds1, a mutation in *Arabidopsis* suppressing resistance to *Peronospora parasitica* specified by several different RPP genes. Plant Cell, 8(11): 2033–2046

Pieterse C M J, Van der Does D, Zamioudis C, Leon-Reyes A, Van Wees S C (2012). Hormonal modulation of plant immunity. Annu Rev Cell Dev Biol, 28(1): 489–521

Pontier D, Miao Z H, Lam E (2001). Trans-dominant suppression of plant TGA factors reveals their negative and positive roles in plant defense responses. Plant J, 27(6): 529–538

Preston F E, Whipps S, Jackson C A, French A J, Wyld P J, Stoddard C J (1981). Inhibition of prostacyclin and platelet thromboxane A2 after low-dose aspirin. N Engl J Med, 304(2): 76–79

Prins T W, Tudzynski P, von Tiedemann A, Tudzynski B, Have A T, Hansen M E, Tenberge K, van Kan J A L(2000). Infection Strategies of *Botrytis cinerea* and related necrotrophic pathogens. Fungal Pathology: p. 33–64

Raskin I (1992). Role of salicylic acid in plants. Annu Rev Plant Physiol Plant Mol Biol, 43(1): 439–462

Raskin I, Skubatz H, Tang W, Meeuse B J D (1990). Salicylic acid levels in thermogenic and non-thermogenic plants. Ann Bot (Lond), 66(4): 369–373

Ross D(2002). Ireland: History of a Nation. Glasgow: Geddes& Grosset.

Saleh A, Withers J, Mohan R, Marqués J, Gu Y, Yan S, Zavaliev R, Nomoto M, Tada Y, Dong X (2015). Posttranslational modifications of the master transcriptional regulator NPR1 enable dynamic but tight control of plant immune responses. Cell Host Microbe, 18(2): 169–182

Scardaci S C(2016). Rice Blast: A New Disease in California. (Web Document)April 5.

Shine M B, Yang J W, El-Habbak M, Nagyabhyru P, Fu D Q, Navarre D, Ghabrial S, Kachroo P, Kachroo A (2016). Cooperative functioning between phenylalanine ammonia lyase and isochorismate synthase activities contributes to salicylic acid biosynthesis in soybean. New Phytologist, 212(3):627–636

Shulaev V, Silverman P, Raskin I (1997). Methyl salicylate–an airborn signal in pathogen resistance. Nature, (6618): 718–721

Slaymaker D H, Navarre D A, Clark D, del Pozo O, Martin G B, Klessig D F (2002). The tobacco salicylic acid-binding protein 3 (SABP3) is the chloroplast carbonic anhydrase, which exhibits antioxidant activity and plays a role in the hypersensitive defense response. Proc Natl Acad Sci USA, 99(18): 11640–11645

Smith W L, Garavito R M, DeWitt D L (1996). Prostaglandin endoperoxide H synthases (cyclooxygenases)-1 and-2. J Biol Chem, 271(52): 33157–33160

Spoel S H, Johnson J S, Dong X (2007). Regulation of tradeoffs between plant defenses against pathogens with different lifestyles. Proc Natl Acad Sci USA, 104(47): 18842–18847

Spoel S H, Mou Z, Tada Y, Spivey N W, Genschik P, Dong X (2009). Proteasome-mediated turnover of the transcription coactivator NPR1 plays dual roles in regulating plant immunity. Cell, 137(5): 860–872

Spoel S H, Mou Z, Zhang X, Pieterse C M J, Dong X (2006). Regulatory Roles of NPR1 in Plant Defense: Regulation and Function. Utrecht University Repository

Strawn M A, Marr S K, Inoue K, Inada N, Zubieta C, Wildermuth M C (2007). *Arabidopsis* isochorismate synthase functional in pathogen-induced salicylate biosynthesis exhibits properties consistent with a role in diverse stress responses. J Biol Chem, 282(8): 5919–5933

Tada Y, Spoel S H, Pajerowska-Mukhtar K, Mou Z, Song J, Wang C, Zuo J, Dong X (2008). Plant immunity requires conformational changes [corrected] of NPR1 via S-nitrosylation and thioredoxins. Science, 321(5891): 952–956

Talbot N J(2003). On the trail of a cereal killer: Exploring the biology of *Magnaporthe grisea*. Annu Rev Microbiol, 57(1): 177–202

Spreen T H (2012). The Economic Impact of HLB on the Florida Citrus Industry, in Food and Resource Economics. University of Florida

Tian M, von Dahl C C, Liu P P, Friso G, van Wijk K J, Klessig D F (2012). The combined use of photoaffinity labeling and surface plasmon resonance-based technology identifies multiple salicylic acid-binding proteins. Plant J, 72(6): 1027–1038

Torres M A, Morales J, Sánchez-Rodríguez C, Molina A, Dangl J L (2013). Functional interplay between *Arabidopsis* NADPH oxidases and heterotrimeric G protein. Mol Plant Microbe Interact, 26(6): 686–694

Trombetta E S, Parodi A J (2003). Quality control and protein folding in the secretory pathway. Annu Rev Cell Dev Biol, 19(1): 649–676

Tsuda K, Katagiri F (2010). Comparing signaling mechanisms engaged in pattern-triggered and effector-triggered immunity. Curr Opin Plant Biol, 13(4): 459–465

Tully J P, Hill A E, Ahmed H M, Whitley R, Skjellum A, Mukhtar M S (2014). Expression-based network biology identifies immune-related functional modules involved in plant defense. BMC Genomics, 15 (1): 421

Van der Does D, Leon-Reyes A, Koornneef A, Van Verk M C, Rodenburg N, Pauwels L, Goossens A, Körbes A P, Memelink J, Ritsema T, Van Wees S C, Pieterse C M (2013). Salicylic acid suppresses jasmonic acid signaling downstream of SCFCOI1-JAZ by targeting GCC promoter motifs via transcription factor ORA59. Plant Cell, 25(2): 744–761

van Loon L C, Rep M, Pieterse C M (2006). Significance of inducible defense-related proteins in infected plants. Annu Rev Phytopathol, 44 (1): 135–162

van Verk M C, Neeleman L, Bol J F, Linthorst H J (2011). Tobacco transcription factor NtWRKY12 interacts with TGA2.2 *in vitro* and *in vivo*. Front Plant Sci, 2(32): 32

Vitale A, Denecke J (1999). The endoplasmic reticulum-gateway of the secretory pathway. Plant Cell, 11(4): 615–628

Wagner S, Stuttmann J, Rietz S, Guerois R, Brunstein E, Bautor J, Niefind K, Parker J E (2013). Structural basis for signaling by exclusive EDS1 heteromeric complexes with SAG101 or PAD4 in plant innate immunity. Cell Host Microbe, 14(6): 619–630

Wang D, Amornsiripanitch N, Dong X (2006). A genomic approach to identify regulatory nodes in the transcriptional network of systemic acquired resistance in plants. PLoS Pathog, 2(11): e123

Wang D, Weaver N D, Kesarwani M, Dong X (2005). Induction of protein secretory pathway is required for systemic acquired resistance. Science, 308(5724): 1036–1040

Wang G Y, Shi J L, Ng G, Battle S L, Zhang C, Lu H (2011). Circadian clock-regulated phosphate transporter PHT4;1 plays an important role in *Arabidopsis* defense. Mol Plant, 4(3): 516–526

Wang W, Barnaby J Y, Tada Y, Li H, Tör M, Caldelari D, Lee D U, Fu X D, Dong X (2011b). Timing of plant immune responses by a central circadian regulator. Nature, 470(7332): 110–114

Wiermer M, Feys B J, Parker J E (2005). Plant immunity: the EDS1 regulatory node. Curr Opin Plant Biol, 8(4): 383–389

Wu C T, Leubner-Metzger G, Meins F Jr, Bradford K J (2001). Class I -1,3-glucanase and chitinase are expressed in the micropylar endosperm of tomato seeds prior to radicle emergence. Plant Physiol, 126(3): 1299–1313

Wu L, Chen H, Curtis C, Fu Z Q (2014). Go in for the kill: How plants deploy effector-triggered immunity to combat pathogens. Virulence, 5(7): 710–721

Xiang C, Miao Z, Lam E (1997). DNA-binding properties, genomic organization and expression pattern of TGA6, a new member of the TGA family of bZIP transcription factors in *Arabidopsis thaliana*. Plant Mol Biol, 34(3): 403–415

Yi S Y, Kwon S Y (2014). How does SA signaling link the Flg22 responses? Plant Signal Behav, 9(11): e972806

Yi S Y, Min S R, Kwon S Y (2015). NPR1 is instrumental in priming for the Enhanced flg22-induced MPK3 and MPK6 activation. Plant Pathol J, 31(2): 192–194

Yin M J, Yamamoto Y, Gaynor R B (1998). The anti-inflammatory agents aspirin and salicylate inhibit the activity of I(kappa)B kinase-beta. Nature, 396(6706): 77–80

Yoshimoto K, Jikumaru Y, Kamiya Y, Kusano M, Consonni C, Panstruga R, Ohsumi Y, Shirasu K (2009). Autophagy negatively regulates cell death by controlling NPR1-dependent salicylic acid signaling during senescence and the innate immune response in *Arabidopsis*. Plant Cell, 21(9): 2914–2927

Yu D, Chen C, Chen Z (2001). Evidence for an important role of WRKY DNA binding proteins in the regulation of NPR1 gene expression. Plant Cell, 13(7): 1527–1540

Zeng W, He S Y (2010). A prominent role of the flagellin receptor FLAGELLIN-SENSING2 in mediating stomatal response to Pseudomonas syringae pv tomato DC3000 in *Arabidopsis*. Plant Physiol, 153(3): 1188–1198

Zhang C, Xie Q, Anderson R G, Ng G, Seitz N C, Peterson T, McClung C R, McDowell J M, Kong D, Kwak J M, Lu H (2013). Crosstalk between the circadian clock and innate immunity in Arabidopsis. PLoS Pathog, 9(6): e1003370

Zhang X, Mou Z (2009). Extracellular pyridine nucleotides induce PR gene expression and disease resistance in *Arabidopsis*. Plant J, 57(2): 302–312

Zhang Y, Fan W, Kinkema M, Li X, Dong X (1999). Interaction of NPR1 with basic leucine zipper protein transcription factors that bind sequences required for salicylic acid induction of the PR-1 gene. Proc Natl Acad Sci USA, 96(11): 6523–6528

Zheng Z, Qamar S A, Chen Z, Mengiste T (2006). *Arabidopsis* WRKY33 transcription factor is required for resistance to necrotrophic fungal pathogens. Plant J, 48(4): 592–605

Zhou J M, Trifa Y, Silva H, Pontier D, Lam E, Shah J, Klessig D F (2000). NPR1 differentially interacts with members of the TGA/OBF family of transcription factors that bind an element of the PR-1 gene required for induction by salicylic acid. Mol Plant Microbe Interact, 13(2): 191–202

Zhou M, Wang W, Karapetyan S, Mwimba M, Marqués J, Buchler N E, Dong X (2015). Redox rhythm reinforces the circadian clock to gate immune response. Nature, 523(7561): 472–476

Zhu S, Jeong R D, Venugopal S C, Lapchyk L, Navarre D, Kachroo A, Kachroo P (2011). SAG101 forms a ternary complex with EDS1 and PAD4 and is required for resistance signaling against turnip crinkle virus. PLoS Pathog, 7(11): e1002318