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MYC2: The Master in Action

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ABSTRACT Jasmonates (JAs) are plant hormones with essential roles in plant defense and development. The basic-helix-loop-helix (bHLH) transcription factor (TF) MYC2 has recently emerged as a master regulator of most aspects of the jasmonate (JA) signaling pathway in *Arabidopsis*. MYC2 coordinates JA-mediated defense responses by antagonistically regulating two different branches of the JA signaling pathway that determine resistance to pests and pathogens, respectively. MYC2 is required for induced systemic resistance (ISR) triggered by beneficial soil microbes while MYC2 function is targeted by pathogens during effector-mediated suppression of innate immunity in roots. Another notable function of MYC2 is the regulation of crosstalk between the signaling pathways of JA and those of other phytohormones such as abscisic acid (ABA), salicylic acid (SA), gibberellins (GAs), and auxin (IAA). MYC2 also regulates interactions between JA signaling and light, phytochrome signaling, and the circadian clock. MYC2 is involved in JA-regulated plant development, lateral and adventitious root formation, flowering time, and shade avoidance syndrome. Related bHLH TFs MYC3 and MYC4 also regulate both overlapping and distinct MYC2-regulated functions in *Arabidopsis* while MYC2 orthologs act as 'master switches' that regulate JA-mediated biosynthesis of secondary metabolites. Here, we briefly review recent studies that revealed mechanistic new insights into the mode of action of this versatile TF.

Key words: ABA; auxin; DELLAs; gibberellin; hormonal crosstalk; jasmonate; JAZ proteins; light signaling; MED25; MYC2; plant defense; phytochrome; *Pseudomonas syringae*; salicylic acid.

INTRODUCTION

The plant hormone jasmonate (JA) plays essential roles in many plant processes ranging from plant defense against pest and pathogens to plant growth and development (Wasternack, 2007). Tremendous progress has been made in recent years towards better understanding of the processes involved in the mode of action of this versatile plant hormone in the reference plant *Arabidopsis thaliana*. As reviewed extensively elsewhere (Balbi and Devoto, 2008; Kazan and Manners, 2008; Staswick, 2008; Browse, 2009; Chini et al., 2009a; Gfeller et al., 2010; Howe, 2010; Pauwels and Goossens, 2011; Wager and Browse, 2012), the primary signal transduction processes following JA perception converge on related bHLH TFs. Of these, the best characterized and most multifunctional is MYC2, which acts as a regulatory hub within the JA signaling pathway. This review presents a mechanistic overview of our current understanding of diverse JA-dependent functions regulated by MYC2.

POSITIONING MYC2 IN JA SIGNAL TRANSDUCTION

Before diverse functions regulated by MYC2 are described, it is important to briefly explain the key position of this TF in the signal transduction processes that regulate JA responses. Under stress-free growth conditions, JA responses are restrained by a group of nuclear proteins called JASMONATE-ZIM-DOMAIN (JAZ) repressors. JAZ repressors interact with both the F-box protein COI1 (CORONATINE INSENSITIVE1), an integral part of the SCF (Skp-Cullin-F-box) complex involved in the co-reception of biologically active JA (Jasmonyl-L-Isoleucine or JA-Ile), as well as with a number of JA-responsive TFs (Chini et al., 2007; Thines et al., 2007; Yan et al., 2007). To repress the transcriptional activity of downstream TFs involved in specific aspects of JA signaling, JAZ proteins recruit co-repressors, such as TOPLESS (TPL) or TPL-related proteins (TRPs), either directly through their EAR (ETHYLENE RESPONSE FACTOR-ASSOCIATED AMPHIFILIC REPRESSION) motifs (Kazan, 2006; Kagale et al., 2010; Shyu et al., 2012) or via NINJA (Novel Interactor of JAZ), an EAR-motif-containing protein (Pauwels et al., 2010). The transcriptional repression

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function of JAZ proteins most likely also involves the recruitment of chromatin modifying proteins. JAZ proteins such as JAZ1, JAZ3, and JAZ9 physically interact with HDA6 (HISTONE DEACETYLASE6) (Zhu et al., 2011), a member of the eukaryotic HDA gene family involved in transcriptional through chromatin condensation. HDA6 also affects JA responses (Wu et al., 2008). A co-dependency between TPL and HDA19 (HISTONE DEACETYLASE19), another member of the HDA family, has also been shown via mutant analysis (Long et al., 2006). Therefore, JAZ-mediated suppression of the JA-mediated transcription most likely involves the establishment of a 'closed' or 'suppressed' chromatin state that excludes JA-responsive TFs from binding to their targets (Figure 1A) (reviewed by Pauwels and Goossens, 2011; Kazan and Manners, 2012; Wager and Browse, 2012).

JAZ repressors seem to have a particularly strong affinity on a number of related basic-helix-loop-helix (bHLH) TFs such as MYC2, MYC3, and MYC4 as well as EGL1 (ENHANCER OF GLABRA3 1), GL3 (GLABRA3), and TT8 (TRANSPARENT TESTA8) involved in both specific and overlapping aspects of JA signaling (Cheng et al., 2011; Fernández-Calvo et al., 2011; Niu et al., 2011; Qi et al., 2011). These TFs share strong sequence homology both in their bHLH and JAZ Interaction Domains (JID) (Toledo-Ortiz et al., 2003; Carretero-Paulet et al., 2010; Fernández-Calvo et al., 2011). Of the TFs targeted by JAZ proteins, MYC2 (At1g32640 also known as JIN1, RD22BP1, ZBF1, RAP1, bHLH6, EN38, or JAI1) is by far one of the best studied ones and now considered as a master regulator of the JA signaling pathway (Woldemariam et al., 2011).

In response to pest and pathogen attack or wounding, JA-Ile is rapidly synthesized in the plant tissue (Staswick and Tiryaki, 2004; Fonseca et al., 2009; Wasternack and Kombrink, 2010). The binding of JA-Ile to JAZ-COI1 co-receptor complexes leads to the removal of JAZ repressors by the 26S proteasome (Chini et al., 2007; Thines, et al., 2007; Yan et al., 2009; Sheard et al., 2010). Destruction of JAZ repressors liberates MYC2 from suppression and, like a maestro, MYC2 orchestrates the expression of early JA-response genes that include diverse JA-responsive TFs involved in the regulation of specific branches of the JA signaling pathway (Figure 1B). To regulate transcription of its target genes, MYC2 forms homo- or heterodimers with related bHLH TFs MYC3 and MYC4 (Fernández-Calvo et al., 2011). MYC2 homo- or heterodimers then bind to the G-box *cis*-acting sequence found in target promoters (Boter et al., 2004; Yadav et al., 2005; Dombrecht et al., 2007). To initiate transcription, MYC2 recruits the Mediator complex through physical interaction with the MED25 subunit of the plant Mediator complex (Kidd et al., 2009; Çevik et al., 2012; Chen et al., 2012a). The Mediator complex, in turn, brings essential components (e.g. RNA polymerase II and general transcription factors or GTFs) of the transcription pre-initiation complex (PIC) to MYC2 target promoters (Çevik et al., 2012; Chen et al., 2012a) (Figure 1B). Chromatin-opening proteins such as GCN5 (GENERAL CONTROL NON-REPRESSIBLE5), a histone acetyl transferase, and SPLAYED (SYD), a SWI2/SNF2 (SWItch/Sucrose NonFermentable)-like protein involved in nucleosome remodeling, are also recruited to MYC2 target promoters (Walley et al., 2008).

Recent studies have significantly advanced our understanding of diverse functions executed by MYC2 within the JA signaling pathway. Emerging evidence also indicates that MYC2 acts as a regulatory hub within phytohormone signaling by integrating a variety of endogenous and exogenous signals that shape plant growth and development. In addition to MYC2, the MYC2-related TFs MYC3 and MYC4 share overlapping as well as distinct roles with MYC2 in JA signaling (Cheng et al., 2011; Fernández-Calvo et al., 2011; Niu et al., 2011). For instance, similarly to MYC2, both MYC3 and MYC4 interact with most, if not all, members of the JAZ family. MYC3 and MYC4 possibly recognize similar *cis*-acting sequences (i.e. G-box and its variants; see below) to MYC2, although the DNA-binding affinity of MYC3 and MYC4 differs from that of MYC2. MYC2 expresses throughout the plant but, in particular, strongly expresses in the root tissue, while MYC3, for instance, seems to be expressing mostly in vegetative and MYC4 in vascular tissues (Fernández-Calvo et al., 2011). Possible mechanistic roles of MYC3 and MYC4 in JA and other phytohormone responses require further analyses and, so far, a more detailed molecular understanding has been obtained on how MYC2 functions as a multifaceted transcriptional regulator. Therefore, while we make several references to MYC3 and MYC4 in this review, our main aim is to present an overview of the recently identified MYC2-regulated functions.

MYC2 STRUCTURAL DOMAINS

MYC2, being a bHLH TF, displays general characteristics of this TF protein family (Toledo-Ortiz et al., 2003; Carretero-Paulet et al., 2010; Pires and Dolan, 2010). In its carboxyl domain, MYC2 contains a bHLH domain conserved in plant bHLH proteins. The HLH domain (Figure 2) consisting of two amphipathic alpha-helices of hydrophobic amino acids joined by a loop region is required to form homo- or heterodimers with other TFs such as the MYC2-related bHLH TFs MYC3 and MYC4 (Fernández-Calvo et al., 2011). The C-terminal leucine zipper domain possibly functions as an additional dimerization domain that affects the specificity of interaction with other TFs (Amoutzias et al., 2008). The basic region of the MYC2 protein containing 15–20 mostly basic amino acids is involved in binding to the G-box (5'-CACGTG-3') found in MYC2 target promoters (Toledo-Ortiz et al., 2003; Carretero-Paulet et al., 2010). In its amino-terminus, MYC2 contains a putative transcriptional activation domain (TAD) (Figure 2) (Fernández-Calvo et al., 2011). As stated above, MYC2 recruits the Mediator complex required for transcription initiation (reviewed by Kidd et al., 2011a) through its TAD, which specifically interacts with the ACID

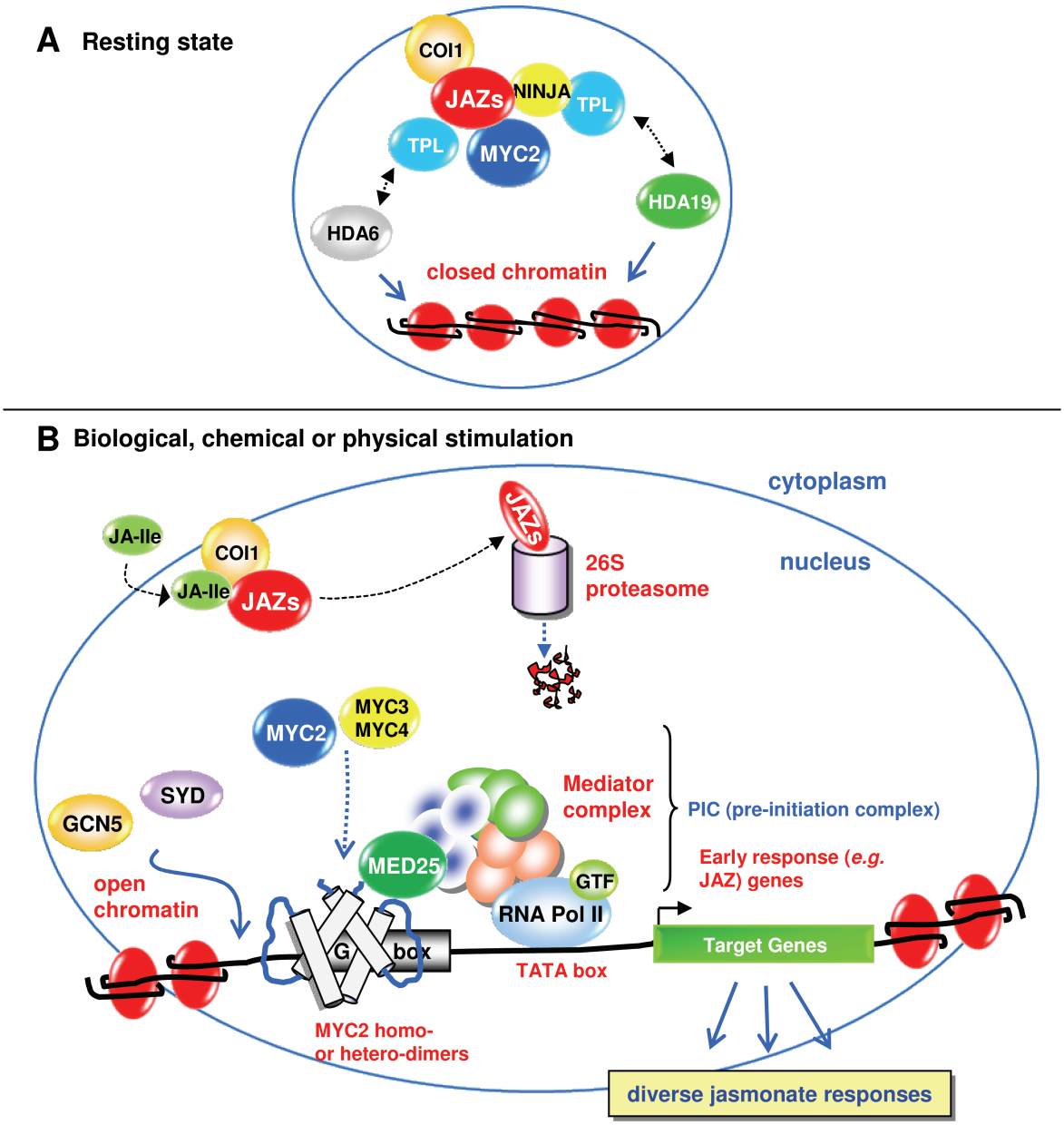

Figure 1. Current View of the MYC2-Mediated Regulation of JA-Responsive Gene Expression.
(A) In the absence of a stimulus, JA-responsive gene expression is suppressed through the action of JAZ proteins, which act as transcriptional repressors of MYC2 and related bHLH TFs MYC3 and MYC4. EAR-motif-containing JAZ repressors directly recruit the co-repressor TOPLESS (TPL) while those that do not contain the EAR motif recruit TPL through the EAR-domain containing protein NINJA (NOVEL INTERATOR OF JAZ). Subsequently, through the action of histone deacetylases (HDAs), a closed chromatin status is achieved and the transcription of JA-responsive genes is inhibited.
(B) JA-Ile rapidly synthesized upon a biological (such as pathogen or insect attack), chemical, or a physical (e.g. wounding) insult is sensed by COI1–JAZ co-receptor complexes. This leads to the proteasome-dependent degradation of JAZ repressors and the release of MYC2, and the related TFs MYC3 and MYC4 from repression. MYC2 forms homo- and/or heterodimers with MYC3 and MYC4 and binds to the conserved G-box present in the promoters of JA-responsive genes. This is followed by the recruitment of chromatin-opening enzymes such as GCN5 (HISTONE ACETYLTRANSFERASE OF THE GNAT FAMILY1) and the SWI/SNF (SWITCH/SUCROSE NONFERMENTING) class protein SPLAYED (SYD). By interacting with the MED25 subunit of the Mediator complex, MYC2 also recruits other components of the transcription pre-initiation complex (PIC), the Mediator complex, RNA Polymerase II, and general transcription factors (GTFs) to target promoters. MYC regulates many diverse JA-dependent plant processes from insect and pathogen defense to plant development (see text for details).

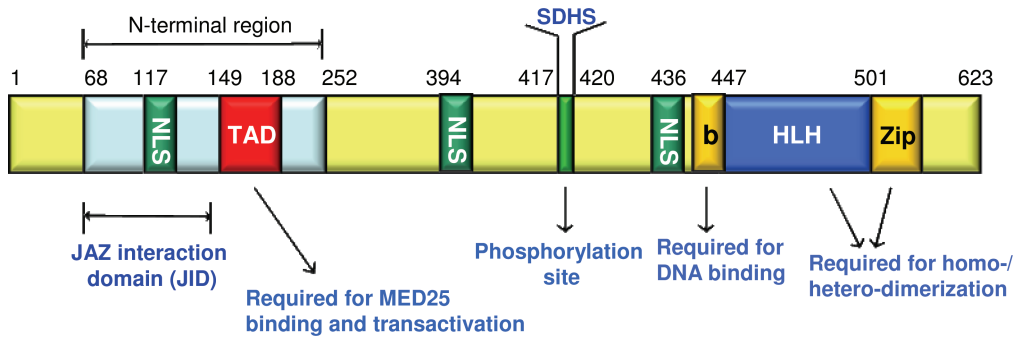

Figure 2. Organization of MYC2 Structural Domains.
JID, the JAZ Interaction domain; TAD, the MYC2 transactivation domain that interacts with the Mediator complex subunit MED25; NLS, nuclear localization signals (PRRR at 117, KRKR at 394, and PKKR at 436) predicted by the pSORT analysis; bHLH, basic-helix-loop-helix domain required for heterodimerization and binding to the G-box sequence in target promoters; Zip, leucine zipper; SDHS, amino acids in the phosphorylation site. Please note that, as indicated in the text, some of the structural domains shown in this figure are not based on experimental analyses, but predicted by either bioinformatic analyses or from conserved functions identified in the members of the bHLH TF gene family. The figure is not drawn to scale. Please see text for additional details.

(ACTIVATOR INTERACTION DOMAIN) and a 10-amino-acid portion of the Middle Domain (MD) of the MED25 subunit of the plant Mediator complex (Çevik et al., 2012; Chen et al., 2012a).

MYC2, MYC3, and MYC4 interact with the C-terminal JAS domain of JAZ proteins through their amino terminal domains called JID (JAZ Interaction Domain) (Chini et al., 2007; Fernández-Calvo et al., 2011). *atr2D*, a previously identified dominant gain-of-function mutant, which constitutively expresses a subset of JA-responsive genes, contains an Asp-to-Asn mutation at the conserved amino acid 94 in the JID of MYC3 (also known as ALTERED TRYPTOPHAN REGULATION2 or ATR2) (Smolen et al., 2002). It was hypothesized that the *atr2d* mutation might interfere with the interaction between MYC3 and JAZ repressors, leading to the constitutive activation of a subset of MYC3-dependent JA responses (Fernández-Calvo et al., 2011; Pauwels and Goossens, 2011).

Protein phosphorylation pathways have been previously implicated in the regulation of JA signaling (Rojo et al., 1998; Takahashi et al., 2007; Hiruma et al., 2011). The MYC2 protein contains a phosphorylation site consisting of serine (S) residues (Figure 2) (Sugiyama et al., 2008). However, the identity of proteins involved in the phosphorylation of MYC2 and possible consequences of this posttranslational modification on MYC2-regulated transcription is still largely unknown.

MYC2 NUCLEAR LOCALIZATION

As expected from a protein involved in gene regulation, MYC2 is a nuclear-localized protein. GFP fused to the C-terminal region of the full-length MYC2 protein is found in the nucleus when transiently expressed in tobacco (*Nicotiana tabacum*) cells (Lorenzo et al., 2004) as well as in stably transformed *Arabidopsis* plants (Chini et al., 2009b). GFP fused to the MYC2 protein missing the bHLH domain displays a localization pattern that is similar to that of the GFP reporter alone, suggesting that the bHLH domain is required for MYC2's nuclear localization (Lorenzo et al., 2004). MYC3 and MYC4 also localize to the nucleus (Cheng et al., 2011; Fernández-Calvo et al., 2011; Niu et al., 2011). However, the exact nature and the location of nuclear localization signal(s) (NLS) required for nuclear targeting of MYC2 are currently unknown. The pSORT analysis of the MYC2 protein identifies at least three putative NLS that reside outside the bHLH domain (Figure 2). It is possible that MYC2 requires dimerization before moving to the nucleus and, therefore, in the absence of its bHLH region, MYC2's nuclear localization may be hindered. Indeed, the *Arabidopsis* bHLH TF PAR1 (PHYTOCHROME RAPIDLY REGULATED1), a regulator of shade avoidance syndrome (SAS), has been shown to have a dual mechanism affecting its nuclear localization. One of the mechanisms is mediated by a non-canonical NLS found at the N-terminus of the PAR1 protein while the other mechanism requires the HLH domain also needed for its dimerization (Galstyan et al., 2012). It is also possible that multiple NLS are concomitantly required for nuclear localization of MYC2. A recent study, for instance, has shown that three non-autonomous NLS act in concert in nuclear targeting of CrMYC2, a MYC2 ortholog regulating the JA-responsiveness of genes involved in the biosynthesis of terpenic indole alkaloids in Madagascar periwinkle (*Catharanthus roseus*) (Hedhili et al., 2010). Mutational analyses of these putative NLS may be required to determine their possible involvement in MYC2's nuclear localization.

MYC2 DNA-BINDING SPECIFICITIES

MYC2 was first isolated based on its strong affinity for the 5'-CACNTG'-3' sequence (de Pater et al., 1997), which is generically referred as the E-box. Subsequent reports have also confirmed that MYC2 binds to the G-box (5'-CACGTG-3') and G-box-related hexamers (Abe et al., 1997; Boter

et al., 2004; Yadav et al., 2005). To identify MYC2 binding site specificities in an unbiased way, high-throughput assays were also employed. In one of such assays, random oligonucleotides were screened for their ability to bind to a MYC2-fusion protein (Dombrecht et al., 2007). In addition to confirming its strong affinity to the G-box, this high-throughput screen identified a number of G-box variants such as 5′-CACATG-3′ and 5′-CACGTG-3′ with significant MYC2-binding activity. Nucleotides such as thymidine (T) residues flanking the core G-box also influenced MYC2 binding activity (Dombrecht et al., 2007). Indeed, the G-box containing 3′-T nucleotides (5′-GACGTG*TTTT*-3′) located at the –68 position in the promoter of the *JAZ2* gene appears to be necessary for JA-dependent activation of *JAZ2* by MYC2 as well as MYC3 and MYC4 (Figueroa and Browse, 2012). The number of T-residues flanking the core G-box sequence also appears to be critical for the activation mediated by this sequence, as the removal of one or more of the Ts reduces the activation of the promoter. The 5′-GACGTG*TTTT*-3′ sequence is conserved in the promoters of *JAZ2* orthologs from at least four other Brassicae species. Furthermore, a genome-wide search has revealed that 25% of early JA-responsive genes (i.e. genes responding to JA treatment within 30 min of JA application) contain this *cis*-acting sequence, providing additional support for the potential importance of this sequence in MYC2-regulated expression of JA-responsive genes (Figueroa and Browse, 2012).

More recently, a protein-binding microarray suitable for accurate and high-throughput quantification of TF-binding sites has also been used for the identification of MYC2 binding sites (Godoy et al., 2011). The G-box was again the major *cis*-acting sequence bound with high activity by MYC2. In addition, a number of other sequences with which MYC2 binds with medium-to-low affinity were also identified. These new MYC2 targets include various G-box variants such as 5′-AACGTG-3′ and 5′-CATGTG-3′ that were also identified in previous studies (Abe et al., 1997; Boter et al., 2004; Chini et al., 2007; Dombrecht et al., 2007) along with new MYC2 targets such as the G/A-box (5′-CACGAG-3′) and the G/C-box (5′-CACGCG-3′). MYC2-binding sequences identified through this protein-binding microarray were also strongly represented in the promoters of MYC2-regulated genes (Godoy et al., 2011). Taken together, these studies establish that G-box-related motifs are the preferred binding sites of MYC2. It is likely that the ability to bind a range of G-box variants significantly broadens the number of potential target genes regulated by this TF. It should also be noted that MYC3 and MYC4 show similar DNA-binding specificities to MYC2 (Fernández-Calvo et al., 2011).

MYC2 AND FINE-TUNING OF THE JA RESPONSE

Acting upstream in the JA signaling pathway, MYC2 fine-tunes the pathway by regulating not only the expression of transcriptional activators that function downstream from MYC2, but also JAZ repressors that act upstream from MYC2. JA-responsive expression of most *JAZ* genes shows reduced expression relative to wild-type plants in the JA-treated *myc2* mutant in response to JA treatment (Chini et al., 2007; Grunewald et al., 2009) and *JAZ* genes are constitutively expressed in plants overexpressing *MYC2* (Chini et al., 2007). Providing additional evidence that MYC2 is a regulator of *JAZ* gene expression, recent studies have demonstrated that MYC2 directly binds to the promoter of at least two *JAZ* genes, *JAZ3* (Chini et al., 2007) and *JAZ2* (Figueroa and Browse, 2012). As stated above, continuous destruction followed by MYC2-mediated transcriptional activation and re-synthesis of JAZ repressors in response to JA stimulation would ensure that activation and subsequent re-closure of the pathway occur in a controlled manner (Chini et al., 2007). A recent study, however, reported very little alteration in the expression of *JAZ* genes in the *myc2* mutant inoculated with the bacterial pathogen *Pst* DC3000 (Demianski et al., 2012), which produces coronatine (COR), a bacterial toxin and also a potent JA-Ile mimic. This unexpected finding was explained by possible involvement of the MYC2-related TFs MYC3 and MYC4 in the regulation of *JAZ* genes. However, *JAZ* gene expression in the *myc2* mutant was examined 24 h and 48 h after bacterial inoculations in this study. It is possible that the effect of the *myc2* mutation on *JAZ* gene expression may have been missed at these relatively late time points.

MYC2 ORCHESTRATES A DOWNSTREAM TRANSCRIPTIONAL CASCADE

The genes that show differential expression in the *myc2* mutant and are thus directly or indirectly regulated by MYC2 during JA signaling (6 h after JA treatment) were identified by comparative microarray analysis of JA-treated and untreated *myc2* and wild-type plants (Dombrecht et al., 2007). These analyses suggested that MYC2 regulates the expression of a large number of JA-responsive genes, including a number of TFs that are involved in specific aspects of the JA signaling pathway (Dombrecht et al., 2007). Based on these gene expression analyses and functional tests, it was found that MYC2 is a positive regulator of insect defense, wound responses, flavonoid metabolism, and oxidative stress tolerance during JA signaling. In contrast, MYC2 negatively regulates the expression of pathogen defense and also secondary metabolism during JA signaling (reviewed by Kazan and Manners, 2008). A recent proteomic analysis of the JA-treated *myc2* mutant have also reported differentially expressed proteins (Guo et al., 2012) that are consistent with MYC2-regulated functions predicted from large-scale transcriptome analyses (Dombrecht et al., 2007).

MYC2 AND TRANSCRIPTIONAL REPRESSION

As stated above, MYC2 acts as both a transcriptional activator and a transcriptional repressor in the regulation of different aspects of JA signaling. Microarray analysis identifies that large numbers of JA-responsive genes expressed significantly higher or lower in the *myc2* mutant than in wild-type plants (Dombrecht et al., 2007). Importantly, genes that are negatively regulated by MYC2 during JA signaling include JA-responsive pathogen defense genes such as *PDF1.2*, *CHIB*, and *PR4* (Anderson et al., 2004; Lorenzo et al., 2004) as well as positive regulators of these defense genes AP2/ERF TFs *ERF1* (*ETHYLENE RESPONSE FACTOR1*) and *ORA59* (*OCTADECANOID-RESPONSIVE ARABIDOPSIS AP2/ERF59* known only as At1g06160 at the time of this previous report by Dombrecht et al., 2007; see also Zander et al., 2010; Verhage et al., 2011). It is currently unknown, however, whether MYC2-mediated suppression of these TFs involves any physical interaction between MYC2 and ERF1 and ORA59 or binding of MYC2 to *ERF1* and *ORA59* promoters. Nevertheless, both *ORA59* (5′-CACGTG-3′) and *ERF1* (5′-CACGTG-3′ and 5′-CACATG-3′) promoters contain putative G-boxes, suggesting that MYC2 may directly bind to the promoter of these genes to regulate their expression. A G-box-like sequence found in the promoter of the *PDF1.2* gene does not show any significant MYC2 binding activity (Dombrecht et al., 2007). This further supports the view that *PDF1.2* is not directly suppressed by MYC2. It is therefore possible that repression of these TFs by MYC2 may not be due to direct protein interactions between MYC2 and ERF1 or ORA59 or transcriptional regulation of these TFs by MYC2, but due to MYC2-mediated regulation of EBF1 (EIN3-BINDING F BOX PROTEIN1), which in turn regulates *EIN3* (*ETHYLENE INSENSITIVE3*) encoding a positive regulator of *ERF1* and *ORA59* (Zhu et al., 2011). More recently, evidence for transcriptional repression possibly occurring through direct promoter binding by MYC2 has been demonstrated for *SPA1* (*SUPPRESSOR OF PHYA-105 1*) (Gangappa et al., 2010) and *PLT1* and *PLT2* (*PLETHORA*) (Chen et al., 2011). The relevance of these genes to MYC2-related functions is discussed in more detail below.

Currently, very little, if anything, is known mechanistically on how transcriptional repression by MYC2 is achieved. A few possible suppression mechanisms may include the dimerization of MYC2 with a repressor-type TF that interferes with the binding of MYC2 to the G-box. Active repression mechanisms may involve the binding of MYC2 to the G-box and the recruitment of co-repressor complexes such as histone deacetylases (HDAC) and DNA methyl transferases to target promoters, while indirect repression mechanisms may include the activation of JA-responsive repressors such as the EAR-motif-containing AP2/ERF TF ERF4 (McGrath et al., 2005). Additional work is required to better understand potential mechanisms involved in MYC2-mediated gene suppression during JA signaling.

THE MYC2 PROTEIN–PROTEIN INTERACTION NETWORK

The MYC2 protein–protein interaction network is now emerging from both experimental and systems biology studies. As indicated earlier, MYC2 interacts with all known JAZ repressors and the MED25 subunit of the plant Mediator complex. MED25 is required for both transcriptional activation and repression activity of MYC2 (Çevik et al., 2012; Chen et al., 2012a). Other known MYC2 interactors are AHP5 (HISTIDINE-CONTAINING PHOSPHOTRANSFER FACTOR5), implicated in cytokinin signaling (Yamashino et al., 2003); TIC (TIME FOR COFFEE) (Shin et al., 2012), a regulator of the circadian signaling; SGB3 (SUPPRESSOR OF G BETA3) (Klopffleisch et al., 2011), an acireductone dioxygenase implicated in heterotrimeric G-protein signaling (Friedman et al., 2011); and all members (RGA, GAI, RGL1, RGL2, and RGL3) of DELLA proteins acting as repressors within GA signaling (Hong et al., 2012). MYC2 also interacts with the RCD1 (RADICAL INDUCED CELL DEATH1) protein. Furthermore, a significant overlap was found between RCD1- and MYC2-regulated genes (Jaspers et al., 2009) and this seems to be consistent with the role of RCD1 in the regulation of diverse hormonal (e.g. JA and ABA) and developmental responses (Ahlfors et al., 2004).

As stated earlier, MYC2 also interacts with the related bHLH TFs MYC3 and MYC4 and forms heterodimers *in vivo* (Fernández-Calvo et al., 2011). The recently constructed *Arabidopsis* regulatory network, AtPAN (Arabidopsis thaliana Promoter Analysis Net, http://atpan.itps.ncku.edu.tw/), predicts more than 100 MYC2 interactors (Chen et al., 2012b). Given the precedence of confirmed interactions between MYC2 and other bHLH TFs (e.g. MYC3 and MYC4), other predicted interactors from the bHLH TF family include a number of uncharacterized (e.g. At5g57150, At1g68920, At3g61950, At1g01260, and At3g57800) as well as relatively well characterized bHLH TFs such as PIF4 (PHYTOCHROME INTERACTING FACTOR4) and PAP3 (PHYTOCHROME-ASSOCIATED PROTEIN3); CIB5 (CRYPTOCHROME-INTERACTING BASIC-HELIX-LOOP-HELIX5), a regulator of cryptochrome signaling; ICE1 (INDUCER OF CBF EXPRESSION1), a regulator of abiotic stress tolerance; BIM1, a regulator of brassinosteroid signaling; as well as ALC (ALCATRAZ), a regulator of plant development (Chen et al., 2012b). Although these predicted interactions require experimental confirmation, it can be speculated that MYC2's dimerization with other bHLH TFs could generate additional functional diversity and thereby contribute to MYC2's regulatory effects on multiple signaling pathways.

MYC2 AND SYSTEMIC SIGNALING

Stimulation of plant defense by a biological or chemical agent prior to pathogen challenge can increase the alertness of the plant to a subsequent attack. Colonization of plant roots by the beneficial rhizobacteria *Pseudomonas*

fluorescens, for instance, increases resistance in the aboveground part of the plant and this phenomenon is known as induced systemic resistance (ISR) (Pozo et al., 2008). In contrast to systemic acquired resistance (SAR), which is primarily regulated by the plant hormone salicylic acid (SA), ISR is dependent on JA and ethylene (ETH) signaling as well as NPR1 (NONEXPRESSER OF PR GENES1), a master regulator of SA signaling (Pieterse et al., 2012). The *myc2* mutant shows defects in rhizobacteria-induced ISR to the bacterial pathogen *Pseudomonas syringae* pv. *tomato* (*Pst*) DC3000 and the fungal pathogen *Hyaloperonospora parasitica*, the causative agent of the downy mildew disease. In addition, the colonization of *Arabidopsis* roots by rhizobacteria primes large numbers of JA-responsive genes in the shoot tissue, containing G-box-like sequences in their promoters (Pozo et al., 2008), suggesting that MYC2 is a regulator of this response.

Microarray analyses showed that transcripts associated with JA biosynthesis and signaling were up-regulated in systemic leaves of *Arabidopsis* previously challenged with the bacterial pathogen *Pst* DC3000 and this was accompanied by the accumulation of JAs in the systemic tissue (Truman et al., 2007). In the *myc2* mutant, the systemic immunity against *Pst* DC3000 carrying the avirulence gene *avrRPM1* was reduced when secondary leaves of the *myc2* mutant were inoculated 2 d later with the same pathogen (Truman et al., 2007). Although this finding supports the view that JA signaling and MYC2 are important components of systemic immunity, a subsequent study reported that *P. s.* pv. *maculicola* pre-inoculated *myc2* mutant retains its ability to develop SAR following inoculation of distal leaves with the same bacteria (Attaran et al., 2009). Therefore, further research is required to determine possible roles of MYC2, if any, in SAR against bacterial and fungal pathogens.

In response to mechanical wounding of roots, MYC2 is systemically and rapidly activated in leaves. Although, the involvement of MYC2 in wound-mediated systemic signaling requires further investigation, promoters of large number of genes systemically induced in the leaf tissue following wounding of the roots were enriched for the G-box-like sequences (e.g. 5′-AACGTG-3′ and 5′-ACGTGG-3′), thereby implying a MYC2-regulated function in the root–shoot signaling phenomenon (Hasegawa et al., 2011).

MYC2 AND JA-MEDIATED SYSTEMIC SUSCEPTIBILITY

The leaves of the *myc2* mutant show increased resistance to the root-infecting fungal pathogen *Fusarium oxysporum* and initially this was explained by negative regulatory effects of MYC2 on JA-dependent defense gene expression (Anderson et al., 2004). In fact, when JA-dependent defenses are either boosted or inhibited by transgenic overexpression of activator or repressor-type AP2/ERF TFs, respectively, a relatively small increase in *Fusarium* resistance has been observed (McGrath et al., 2005). However, subsequent experiments showed that disease symptom development, even in the presence of fungal infection, was nearly absent in the *coi1* mutant with abolished JA-dependent pathogen defense (Thatcher et al., 2009). Increased resistance to *F. oxysporum* was not due to hyper-activated SA responses in the *coi1* mutant either. It was therefore suggested that the pathogen-induced chlorosis/necrosis, which also seems to be promoted by the host JA signaling pathway, is a major contributor to the susceptibility against this pathogen (Thatcher et al., 2009). Indeed, both *coi1* and *myc2* mutants show reduced sensitivity to chlorosis and necrosis-inducing factors present in the culture filtrates of the pathogen *F. oxysporum* (Thatcher et al., 2012). It is therefore possible that the increased *Fusarium* resistance phenotype observed in the *myc2* mutant (Anderson et al., 2004) may be due to a combination of elevated JA-dependent pathogen defense as well as reduced JA sensitivity, which attenuates pathogen-induced lesion development. In contrast, the increased resistance observed in the *myc2* mutant against leaf-infecting necrotrophs *Botrytis cinerea* and *Plectosphaerella cucumerina* is most likely due to elevated JA-dependent defenses (Lorenzo et al., 2004).

MYC2 AND THE SUPPRESSION OF MAMP-TRIGGERED INNATE IMMUNITY IN *ARABIDOPSIS* ROOTS

Perception of Microbe-Associated Molecular Patterns (MAMPs) such as the flagellar peptide Flg22, peptidoglycan (a component of the bacterial cell wall), and chitin (a fungal cell wall component) by *Arabidopsis* roots results in the activation of innate immune responses such as the production of callose (a β-1–3-glucan polymer) at the root elongation zone and the exudation of phytoalexin camalexin from the root tips. Flg22 treatment of *Arabidopsis* roots activates the expression of *MYB51* (Millet et al., 2010) encoding a MYB TF required for the production of 13G indole-glucosinolates (Gigolashvili et al., 2007) and callose deposition, and the expression of *CYP71A12*, a cytochrome P450 required for phytoalexin biosynthesis.

Both pathogens and beneficial microbes have evolved to suppress MAMP-activated defenses thorough the production of effector molecules as they colonize plant roots (Zamioudis and Pieterse, 2012). For instance, coronatine (COR) (a toxin and a structural JA-Ile analog) produced by the bacterial pathogen *Pst* DC3000 inhibits MAMP (e.g. Flg22)-mediated activation of innate responses such as callose deposition and camalexin production in the roots. MYC2 is required for the suppression of Flg22-mediated activation of immune responses by COR as, in contrast to wild-type roots, Flg22-mediated activation of *MYB51* and *CYP71A12* could not be suppressed by COR in *myc2* roots (Figure 3) (Millet et al., 2010).

The beneficial bacteria *Pseudomonas fluorescens* WCS417r, which triggers ISR in *Arabidopsis*, seems to have a similar suppressive effect on MAMP-activated root defenses and this suppression also requires MYC2 function (Millet et al., 2010). The colonization of roots by the beneficial fungus *Priformospora indica* is also reduced in the *myc2* mutant, suggesting that MYC2 is also required for the attenuation of root defenses by unknown fungal effectors (Jacobs et al., 2011).

MYC2 AND JA-DEPENDENT DEFENSE AGAINST HERBIVORY

MYC2 is a positive regulator of the insect defense gene *VSP* and the *myc2* mutant shows an increased susceptibility to the cotton bollworm pathogen *Helicoverpa armigera* larvae (Dombrecht et al., 2007). Recent studies suggest another role for MYC2 as part of a defense strategy against the generalist insect *Pieris rapae*. Interestingly, this role appears to be independent of MYC2's positive regulatory roles on JA-dependent insect defenses but is executed through the suppressive effect of MYC2 on the ORA59-regulated branch of JA signaling which is required for resistance to necrotrophic fungal pathogens. Interestingly, recent evidence has suggested that the ORA59 branch of JA signaling promotes the attractiveness of *Arabidopsis* to *P. rapae* by an unknown mechanism (Verhage et al., 2011). Indeed, when the *P. rapae* larvae were given the choice to feed on either *myc2* or wild-type plants, the *myc2* mutant, where the ORA59-regulated branch of JA signaling was no longer suppressed, was preferred by the insect. Remarkably, the preference of *myc2* plants by the insect was not due the reduction of insect defenses (e.g. *VSP* expression) in the *myc2* mutant because plants deficient in both MYC2 and ORA59 (*myc2/RNAi-ORA59* plants) and wild-type plants were all equally preferred by the insect, while *ORA59*-overexpressing plants (*35S:ORA59*) were preferred more by the insect than wild-type plants (Verhage et al., 2011). Together, these results suggest that MYC2 controls JA-dependent insect defenses by activating insecticidal genes while also suppressing genes that increase attractiveness of the plant to insects. It is plausible that a combination of different plant defense strategies ensures a broader spectrum of resistance against diverse pests that use different herbivory tactics.

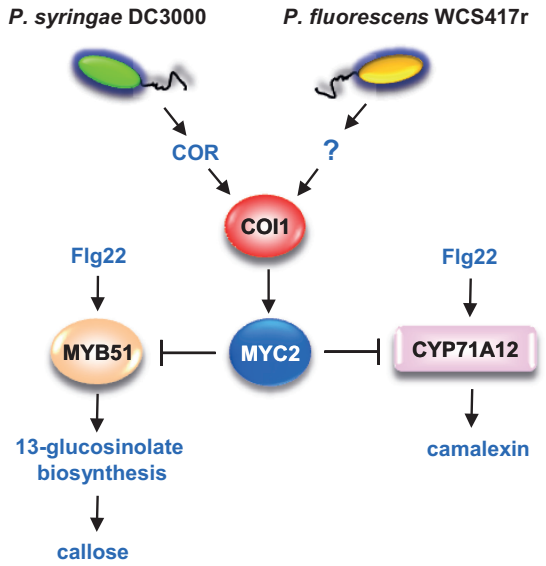

Figure 3. MYC2 Is Required for the Suppression of Microbe-Associated Molecular Patterns (MAMPs)-Activated Defenses by Pathogenic and Beneficial Microbes.

Flg22, a conserved MAMP, activates MYB51-regulated indole glucosinolate biosynthesis, which is required for callose formation and CYP71A12-mediated biosynthesis of the phytoalexin camalexin in *Arabidopsis* roots. Coronatine (COR) a toxin and a JA mimic produced by the bacterial pathogen *P. syringae* DC3000 suppresses these defenses via MYC2, which acts as a negative regulator of MYB51 and CYP71A12. The beneficial bacteria *P. fluorescens* WCS417r-mediated suppression of root innate immunity also requires MYC2 although possible effectors indicated by '?' is currently unknown. See text for details.

THE ROLES OF MYC2 IN ABA SIGNALING

MYC2 is an ABA and drought-responsive gene and therefore earlier studies have focused on the role of MYC2 in ABA signaling. Indeed, *MYC2* overexpressing plants and the *myc2* mutant show increased and reduced ABA sensitivity, respectively (Abe et al., 2003; Lorenzo et al., 2004). Furthermore, transactivation assays show that MYC2 is capable of activating the expression of the ABA response gene *RD22* (*RESPONSIVE TO DESSICATION22*) (Abe et al., 2003), suggesting that MYC2 is a positive regulator of ABA signaling. Transgenic plants overexpressing both *MYC2* and *MYB2*, a drought-inducible MYB TF, show reduced electrolyte leakage following mannitol treatment, suggesting that MYC2 can contribute to stress tolerance (Abe et al., 2003). In contrast, a recent study found an increased drought tolerance in the *myc2* mutant based on smaller relative biomass reduction observed under drought conditions than in wild-type plants (Harb et al., 2010). Therefore, the role of MYC2 in abiotic stress tolerance is not as conclusive as its role in ABA signaling.

The recently identified *DWA* (DWD–DDB1 binding WD40-hypersensitive to ABA) genes *DWA1*, *DWA2*, and *DWA3* all encoding potential receptors for CUL4 E3 ligase complexes act as negative regulators of ABA signaling. MYC2 protein and transcript accumulation and *RD22* transcript levels significantly increase in *dwa* mutants after ABA treatment (Lee et al., 2010, 2011), suggesting that negative regulatory effects of these proteins are exerted at least in part through the suppression of positive regulators of ABA signaling such as MYC2. However, yeast 2H interaction studies did not reveal any physical interaction between MYC2 and DWAs and therefore it is likely

that MYC2 is not a direct substrate for DWA-associated protein degradation pathway (Lee et al., 2010, 2011).

MYC2 AND THE REGULATION OF PHYTOHORMONE CROSSTALK

JA–ABA Crosstalk

Having roles in both JA and ABA signaling, MYC2 also regulates the interaction between these two signaling pathways. As mentioned above, MYC2 acts as both a positive and a negative regulator within the JA signaling pathway. Within ABA signaling, however, so far, only positive regulatory functions have been reported for MYC2. Interestingly, similarly to MYC2, ABA differentially affects different branches of the JA signaling pathway (Figure 4). First, ABA negatively regulates the *ERF1/ORA59-PDF1.2* branch of the JA pathway required for pathogen defense. ABA treatment causes rapid (within 30 min of application) suppression of basal transcript levels of JA-responsive TFs *ERF1* and in particular *ORA59* (Winter et al., 2007; Supplemental Figure 1). ERF1 and ORA59 act as positive regulators of *PDF1.2* (Lorenzo et al., 2003; Pre et al., 2008) and, therefore, the suppression of transcript levels of these TFs by ABA provides a plausible explanation for why *PDF1.2* expression is also suppressed by exogenous ABA (Anderson et al., 2004). During JA signaling, the negative regulatory effects of *MYC2* on *PDF1.2* expression also seem to occur via negative regulation of *ERF1* and *ORA59* by MYC2 (Dombrecht et al., 2007; Zander et al., 2010; Verhage et al., 2011).

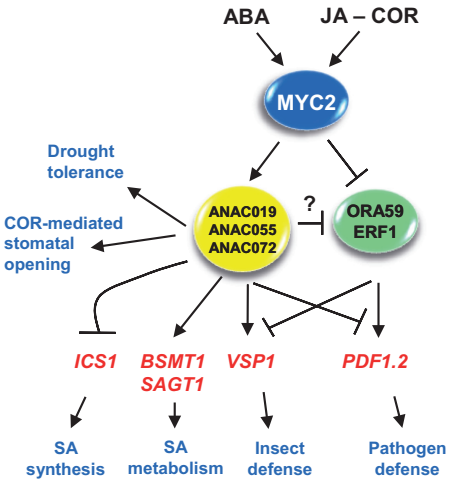

Figure 4. MYC2 and the Regulation of Complex Crosstalk between JA and ABA and JA and SA Signaling.
Both ABA and JA positively regulate the JA-responsive expression of the insect defense gene VSP1 through the MYC2-regulated NAC-domain containing TFs ANAC019 and ANAC055. In contrast, ABA negatively regulates the expression of the JA-responsive pathogen defense gene *PDF1.2* by activating MYC2, which then negatively regulates the AP2/ERF TFs ORA59 and ERF1, known positive regulators of *PDF1.2*. MYC2, in response to coronatine (COR), activates the NAC-domain containing TFs *ANAC019*, *ANAC055*, and *ANAC072*, and these TFs in turn suppresses salicylic acid levels by activating the SA metabolism genes *BSMT1* and *SAGT1* and by suppressing the SA biosynthesis gene ISC1 (*ISOCHORISMATE SYNTHASE1*). See text for details.

In contrast to its suppressive effects on the *ERF1/ORA59-PDF1.2* branch of the JA signaling pathway, ABA positively regulates the *MYC2-VSP1* branch of the JA signaling pathway. ABA strongly induces the expression of *MYC2* as well as that of the NAC-domain containing TF genes *ANAC019* and *ANAC055* (Supplemental Figure 1; Tran et al., 2004; Jiang et al., 2009; Jensen et al., 2010). The ABA-inducibility of both *ANAC019* and *ANAC055* is reduced in the *myc2* mutant (Jiang et al., 2009), suggesting that these two TFs act downstream from MYC2. Both *ANAC019* and *ANAC055* transcript levels are also strongly induced by JA (Winter et al., 2007; Bu et al., 2008; Supplemental Figure 1) in a MYC2-dependent manner (Bu et al., 2008), further suggesting that ANAC019 and ANAC055 act downstream from MYC2 in both ABA and JA signaling. Indeed, similarly to MYC2, ANAC055 and ANAC019 were shown to be positive regulators of *VSP* and negative regulators of *PDF1.2* (Bu et al., 2008). Finally, the finding that the JA-dependent induction of *VSP1* is abolished in the leaves of the ABA biosynthesis mutant *aba2* (Hossain et al., 2011) further implicates the presence of a positive crosstalk between ABA signaling and insect defense activated by JA in a MYC2-dependent manner. Collectively, these findings are consistent with a model where the *MYC2-ANAC019-ANAC015* branch of the JA pathway leading to the expression of the insect defense gene *VSP1* is positively regulated by both ABA and MYC2, whereas the *ERF1-ORA59*-regulated branch of the JA pathway leading to the expression of the pathogen defense gene *PDF1.2* is negatively regulated by both ABA and MYC2 (Figure 4).

As expected, the crosstalk between JA and ABA signaling regulated by MYC2, ANAC019, and ANAC015 would have implications on biotic and abiotic stress responses. For instance, similarly to the *myc2* mutant (Lorenzo et al., 2004), the *anac019 anac055* double mutant shows increased resistance to the necrotrophic fungal pathogen *B. cinerea*, whereas transgenic plants expressing either *ANAC019* and *ANAC055* show increased susceptibility to *B. cinerea* (Bu et al., 2008) but increased resistance to drought (Tran et al., 2004). These findings indicate that MYC2 acts as a master switch regulating both positive and negative interplay between ABA and JA signaling.

JA–SA Crosstalk

Mutually antagonistic crosstalk has been reported between SA and JA signaling in *Arabidopsis* (see Thaler et al., 2012, for a recent review). In particular, SA suppresses JA-mediated induction of *PDF1.2*. The related TGA TFs TGA2 and TGA5 that are positive regulators of JA-dependent expression of defense genes such as *CHIB* (*BASIC CHITINASE*) and *PDF1.2* together with MYC2 acting as a negative regulator of these genes seem to have an effect on SA–JA crosstalk as the suppressive effect of SA on JA inducibility of *PDF1.2* was abolished in the *tga2 tga5 tga6 myc2* quadruple mutant. Although the actual mechanisms of this interplay is not clear, this finding has led to the proposal that the antagonistic effect of SA on JA

pathways is at least partly dependent on the opposing effects of TGA factors and MYC2 on JA-induced plant defense gene expression (Zander et al., 2010).

EDR1 (ENHANCED DISEASE RESISTANT 1), a protein kinase with similarity to MAPKKKs, is an important regulator of SA signaling in *Arabidopsis*. The *edr1* mutant has a hyper-activated SA signaling and shows increased resistance against *Golovinomyces cichoraceaum*, a host-adapted fungal pathogen that causes powdery mildew disease on *Arabidopsis*. The JA-regulated *PDF1.2* and related defensins are down-regulated in the *edr1* mutant (Hiruma et al., 2011), suggesting that EDR1 acts as a positive regulator of JA signaling. MYC2 seems to be acting genetically upstream from EDR1, as increases observed in the pathogen-induced expression of *PDF1.2* in the *myc2* mutant were largely restored in the *edr1 myc2* double mutant. It was proposed that EDR1, belonging to the Raf-like sub-family of MAPKKKs, may inactivate MYC2 through phosphorylation following its release from JAZ suppression (Hiruma et al., 2011).

Finally, based on the analysis of the *myc2* mutant, which displays elevated SA biosynthesis and responses, MYC2 seems to act as a negative regulator of the SA pathway (Nickstadt et al., 2004; Laurie-Berry et al., 2006). The bacterial toxin coronatine (COR) produced by *Pst* DC3000 acts as a JA-Ile mimic to activate the JA signaling pathway. Because of its sensitivity to SA-mediated host defenses, it is thought that *Pst* DC3000 takes advantage of the mutually antagonistic crosstalk between SA and JA signaling to promote disease on *Arabidopsis*. Possible roles of MYC2 in *Pst* DC3000-mediated suppression of the SA has recently been elucidated. It appears that MYC2 binds to the G-box motif found in the promoters of NAC TFs ANAC019, ANAC055, and ANAC072, and activates their expression. These NACs then differentially regulate the expression of genes involved in SA biosynthesis and metabolism. For instance, the expression of the *ICS1* (*ISOCHORISMATE SYNTHASE GENE1*) involved in SA biosynthesis is down-regulated by these NACs, while those of *SAGT1* (*SA GLUCOSYL TRANSFERASE GENE1*), which encodes an enzyme that glucosylates and converts SA to an inactive form, as well as *BSMT1* encoding a methyltransferase that methylates salicylic acid, are up-regulated by these NACs (Zheng et al., 2012). Subsequently, this leads to compromised SA-dependent defenses and enhanced bacterial colonization (Figure 4).

JA–GA Crosstalk

Both antagonistic and synergistic interactions have so far been reported between JA and GA signaling (reviewed by Kazan and Manners, 2012). The major players involved in the crosstalk between these two signaling pathways are DELLA proteins acting as suppressors of GA signaling, JAZ repressors, and MYC2. At low GA levels, DELLAs interact with JAZ1 and this interferes with the suppressive effects of JAZ1 on MYC2, allowing MYC2 to modulate the expression of JA-response genes (Hou et al., 2010; Figure 5A). The increased JA-responsive gene expression observed in *della* mutants is consistent with this proposal. Presumably, when GA levels reach a critical threshold, DELLA proteins are ubiquitinated and this releases JAZ1 from repression, making it available to interact with MYC2 and suppress its transcriptional activity. As stated earlier, this leads to the suppression of MYC2-dependent JA responses. As a consequence of neutralizing the repressive effects of JAZs, DELLAs enhance the strength of binding of MYC2 to its target promoters (Hou et al., 2010). Interestingly, it was also found that, during JA signaling, MYC2 activates the expression of the DELLA protein RGA-LIKE3 (RGL3) by directly binding to the promoter of this gene. RGL3 then interacts with JAZ repressors and this contributes to JAZ repression and the activation of JA-responsive genes in a positive feedback loop regulated by MYC2 (Wild et al., 2012). This delicate balance between GA and JA signaling allows the plant to invest either into growth when the conditions are suitable or into defense when threatened by an

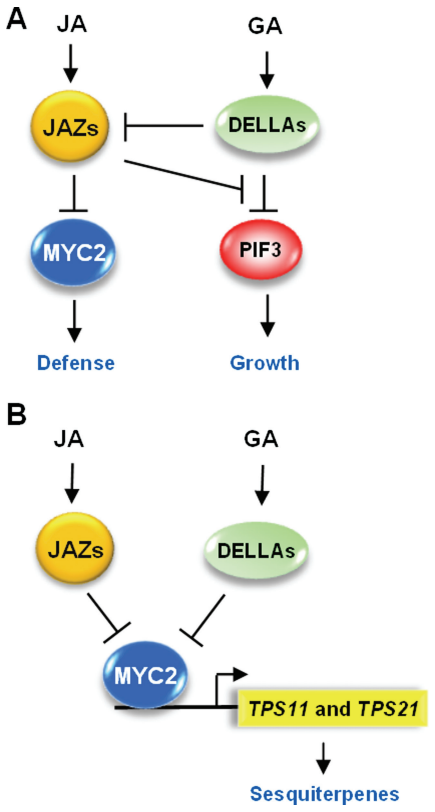

Figure 5. MYC2 Is Involved in Both Negative and Positive Interactions between JA and GA Signaling.
(A) JAZ repressors, by interacting with DELLA proteins, interfere with the repressing activity of DELLAs on *PIF3* (*PHYTOCHROME INTERACTING FACTOR3*) and this promotes growth. In contrast, DELLAs, by interacting with JAZ repressors, contribute to the activation of MYC2 and JA-mediated defense responses.
(B) MYC2 is required for both JA- and GA-mediated activation of *TPS11* and *TPS12* (*TERPENE SYNTHASE11* and *12*) genes involved in the biosynthesis of anti-insecticidal and volatile sesquiterpenes that are emitted from *Arabidopsis* inflorescences. See text for further details.

attacker (Ballaré, 2011; Kazan and Manners, 2011, 2012; Yang et al., 2012).

More recently, a new role for MYC2 as an integrator of signals from both JA and GA pathways has also been reported. MYC2 appears to be a positive regulator of both JA- and GA-responsive expression of the sesquiterpene synthase biosynthesis genes *TPS11* and *TPS12* (Hong et al., 2012) required for the synthesis of volatile, anti-insecticidal compounds emitted from *Arabidopsis* inflorescences. In addition to the previously known interaction between JAZ proteins and MYC2, it appears that DELLA proteins (e.g. RGA or REPRESSOR OF GAI1-3) interact with MYC2 and repress its activity. GA-mediated destruction of DELLAs leads to the release of MYC2 from repression. MYC2, by directly binding to the G-box-like motifs (5′-CATATG-3′) found in the promoters of *TPS11* and *TPS12*, activates their expression (Hong et al., 2012; Figure 5B). Together, these findings indicate that the interaction between JA and GA signaling can be positive or negative and MYC2 has roles in regulating either interaction.

Both positive and negative interactions have also been reported between JA and auxin (IAA) signaling (Kazan and Manners, 2009; Kidd et al., 2011b). For instance, both hormones positively affect lateral root formation (Grunewald et al., 2009; Sun et al., 2009). In contrast, adventitious root formation in *Arabidopsis* is negatively and positively affected by JA and auxin signaling pathways, respectively (Gutierrez et al., 2012) in a MYC2-dependent manner.

MYC2 AND THE REGULATION OF CROSSTALK BETWEEN JA, THE CIRCADIAN CLOCK, LIGHT, AND PHYTOCHROME SIGNALING

Emerging evidence implicates JAs as regulators of both light and circadian signaling (Kazan and Manners, 2011; Goodspeed et al., 2012; Shin et al., 2012). Far Red light (FR) inhibits photomorphogenesis (e.g. hypocotyl elongation) in *Arabidopsis*. The *myc2* mutant shows an attenuated growth inhibition when grown under continuous FR, as the hypocotyl length of the *myc2* mutant was less strongly inhibited relative to its dark-grown counterpart than that in wild-type plants grown under comparable conditions. This suggests that MYC2 is involved in FR responses (Robson et al., 2010). Plants grown under low R/FR ratios, which mimic the competition from nearby plants, display increased stem elongation and this response is known as 'Shade Avoidance Syndrome' or SAS (reviewed by Kazan and Manners, 2011). Similarly to *phyA* mutants, the *myc2* mutant shows an enhanced SAS response manifested by increased hypocotyl length when grown under low R/FR ratios but not under high R/FR ratios (Robson et al., 2010). This differential response of the *myc2* mutant to different R/FR ratios was reminiscent of responses displayed by the *phyA* mutant (Smith et al., 1997), suggesting an interplay between JA and phytochrome signaling. Interestingly, phyA is required for JA-mediated induction of *VSP1*, which is positively regulated by MYC2 (Robson et al., 2010). phyA is also required for JAZ1 degradation by JA, thus explaining why *VSP1* induction by MYC2 requires phyA (Robson et al., 2010). Another piece of evidence for MYC2's involvement in both JA and light signaling comes from the observation that JA- and Red-light inducibility of the *Arabidopsis* sesquiterpene biosynthesis genes *TPS11* and *TPS21* are strongly attenuated in the *myc2* mutant (Hong et al., 2012). These findings are consistent with the view that MYC2 coordinates a complex web of interactions during the regulation of plant growth and development by light quality.

The plant circadian clock, which operates together with the components of light signaling (reviewed by Herrero and Davis, 2012), not only manages the rhythmic (diurnal) responses, but also has a profound effect on plant defense against pathogens (Bhardwaj et al., 2011; Shin et al., 2012). Recent evidence shows that JA biosynthesis in *Arabidopsis* is controlled by the circadian clock, going up during the day and reaching a maximum at midday and then declining again in the afternoon (Goodspeed et al., 2012; Figure 6). *MYC2* expression seems to be under control of the circadian clock, with increased transcript levels at dusk both under diurnal (12-h day/12-h night) and continuous light conditions. The MYC2 protein accumulation also follows a rhythmic accumulation, going up during the day and down during the night (Shin et al., 2012). Furthermore, TIME FOR COFFEE (TIC), a component of the *Arabidopsis* circadian gating of light responses, interacts with MYC2 leading to the proteasome-mediated degradation of the MYC2 protein. The *tic* mutant shows opposite JA-associated phenotypes to the *myc2* mutant, such as increased JA sensitivity, increased susceptibility to *Pst* DC3000, and increased expression of the wound- and insect-responsive genes, *VSP* and *TAT* (*TYROSINE AMINO TRANSFERASE*), but reduced expression of the pathogen defense genes *PDF1.2* and *PR4*, suggesting that MYC2 and TIC differentially affect the same branches of the JA signaling pathway (Shin et al., 2012; Figure 6).

Other evidence for the involvement of MYC2 in light and circadian clock signaling is the recent link observed between MYC2 and SPA1 (SUPPRESSOR OF PHYTOCHROME A-105 1), a protein that is involved in regulating circadian rhythms and light signaling (Ishikawa et al., 2006). MYC2 directly binds to the G-box found in the *SPA1* promoter and regulates its expression (Gangappa et al., 2010). Interestingly, genetic analyses suggested that MYC2 and SPA1 can act both synergistically and antagonistically within the JA signaling pathway. For instance, in contrast to *myc2*, the JA-treated *spa1* mutant displays higher expression of *VSP1* but lower expression of *CHIB* than wild-type plants. MYC2 and SPA1 also show opposite effects on light-regulated expression of *CAB* (*CHLOROPHYLL A/B BINDING PROTEIN*) and *RBCS* (*RIBULOSE BISPHOSPHATE CARBOXYLASE*) genes. In contrast, MYC2 and SPA1 act redundantly in the dark but additively or synergistically in the light to suppress photomorphogenesis (Gangappa et al., 2010). Finally, similarly to the *myc2* mutant, *Arabidopsis hy1* and *hy2* mutants, which are impaired in phytochrome

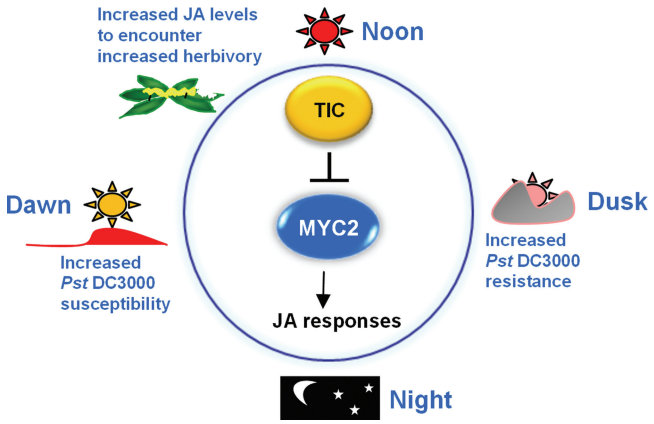

Figure 6. MYC2 and the Interaction between JA and the Circadian Clock Signaling.
JA levels in *Arabidopsis* follow a diurnal pattern, increasing early during the day, reaching a maximum by noon and then decreasing again. This pattern may have evolved to meet the plant's defensive needs against certain herbivores which show increased activity during the day. Increased JA responses make the plant more susceptible to the COR-producing bacterial pathogen *Pst* DC3000, which exploits the plant's JA signaling to cause disease. TIC (TIME FOR COFFEE), a component of the plant's circadian clock, by interacting with MYC2 and repressing its protein accumulation, acts as a regulator of JA responses. See text for details.

chromophore biosynthesis, show reduced sensitivity to JA-mediated root growth inhibition (Costigan et al., 2011). More recently, new functional links between HY1 and MYC2 were identified through the analysis of the *hy1 myc2* double mutant. For instance, it was found that MYC2 works downstream from HY1 in JA-mediated inhibition of root growth (Prasad et al., 2012). Together, these findings further imply the existence of an intimate crosstalk regulated by MYC2 between light and JA signaling.

MYC2 AND PLANT DEVELOPMENT: MYC2 AND JA-MEDIATED ROOT GROWTH INHIBITION

Exogenous JA inhibits primary root elongation and this property has been exploited for the identification of key JA signaling genes including MYC2 (see Browse, 2009, for a review). A recent study showed that JA inhibits cell division in the meristematic cells of *Arabidopsis* primary root in a MYC2-dependent manner (Chen et al., 2011). It appears that, in response to JA, MYC2 binds to the G-box found in the promoters of *PLETHORA* genes, *PLT1* and *PLT2*, and suppresses their expression (Chen et al., 2011). *PLT1* and *PLT2* encode related auxin-responsive AP2/ERF TFs required for maintaining root stem cell activity (Aida et al., 2004). The suppression of these TFs by MYC2 appears to be contributing to the JA-mediated root growth inhibition (Chen et al., 2011).

JAs promote lateral root (LR) formation (Grunewald et al., 2009; Sun et al., 2009) and MYC2 with strong root-specific expression acts as a positive regulator of this process (Yadav et al., 2005). SPA1 is also required for this JA-mediated response. Based on the analysis of lateral root numbers in *myc2* and *spa1* single mutants as well as the *myc2 spa1* double mutant, it was shown that MYC2 and SPA1 (SUPPRESSOR OF PHYTOCHROME A-105 1), a regulator of phytochrome signaling, act additively in the regulation of JA-mediated LR formation as the *myc2 spa1* double mutant shows a more reduced number of lateral roots than either single mutant in the presence of JA (Gangappa and Chattopadhyay, 2010; Gangappa et al., 2010). In contrast to its positive effects on LR formation, the JA pathway and MYC2 negatively regulate adventitious root formation in *Arabidopsis* and this response involves JA–auxin crosstalk (Gutierrez et al., 2012).

MYC2 ORTHOLOGS AND THE REGULATION OF JA-DEPENDENT SECONDARY METABOLITE SYNTHESIS

The roles of JA in the regulation of genes involved in plant secondary metabolite biosynthesis are well established, and are of particular interest in plant cells that produce novel bioactive compounds (Yamada et al., 2011; De Geyter et al., 2012). In JA-treated *Arabidopsis* plants, MYC2 acts as a positive regulator of flavonoid (e.g. anthocyanin) biosynthesis most likely by positively regulating TFs involved in the regulation of flavonoid biosynthetic gene expression (Dombrecht et al., 2007). In contrast, MYC2 negatively regulates JA-responsive biosynthesis of Trp-derived indole-glucosinolates (Dombrecht et al., 2007). MYC2 orthologs from tobacco species (NbbHLH1 and NbBHLH2 from *Nicotiana benthamiana* and NtMYC2 from *N. tabacum*) regulate the expression of nicotine biosynthesis genes in the roots (Todd et al., 2010). These MYC2-like proteins bind to the G-box sequence found in the promoter of the *PMT* gene encoding a putrescine N-methyltransferase. NtMYC2 also activates *ERF189/ORC1*, an AP2/ERF TF, which in turn binds to the GCC-box found in the promoter of the *PMT1* gene. Therefore, the activation of nicotine biosynthesis in tobacco requires collaborative action of both MYC and ERF TFs (De Boer et al., 2011). Similarly to MYC2, NtMYC2 shows the strongest binding activity to the G-box, followed by the 5′-CACGTT-3′ (~35% of binding activity of 5′-CACGTG-3′) and 5′-CACATG-3′ (~20% of binding activity of 5′-CACGTG-3′) sequences (Shoji and Hashimoto, 2011). A similar process involving the MYC2 homolog CrMYC2 and the AP2/ERF TF ORCA (Octadecanoid-Responsive Catharanthus AP2/ERF-domain) operates in the regulation of alkaloid biosynthesis in *Catharanthus roseaus* (Zhang et al., 2011), indicating conserved functions ascribed to MYC2-like genes in these species.

CONCLUSIONS AND FUTURE PERSPECTIVES

The recent findings reviewed in this paper indicate that MYC2 is a master regulator within the JA signaling pathway and

controls a wide range of responses to the biotic and abiotic environment as well as several developmental programs. Acting relatively upstream in the signaling pathway, MYC2 both positively and negatively regulates diverse functions within the JA signaling pathway. The ability to physically interact with other key regulatory proteins, to form heterodimers with other TFs, as well as its ability to activate or repress gene expression in response to multiple signals can all contribute to the diversity of regulatory roles performed by MYC2.

Although MYC2 appears to regulate the expression of a large number of genes containing G-box-like sequences in their promoters during JA signaling (Dombrecht et al., 2007; Pozo et al., 2008; Figueroa and Browse, 2012), currently, relative little is known about whether MYC2 directly binds to the promoters of these genes. Given that MYC2 mainly controls the expression of early JA genes, some of the effects exerted by MYC2 may not be direct effects, but indirectly mediated by MYC2, owing to a cascading effect on other downstream TFs which in turn regulate other JA-responsive genes. Additional studies such as chromatin immunoprecipitation (ChIP) sequencing analyses are needed for genome-wide identification of direct MYC2 targets. It should also be noted that heterodimers formed between two interacting TFs can potentially recognize different *cis*-acting sequences than those by either TF (Amoutzias et al., 2008). In the case of MYC2, this possibility has not been investigated (see also Figueroa and Browse, 2012).

Although several general mechanisms are proposed, currently, very little is known how MYC2-mediated gene repression occurs. A few potential repression mechanisms proposed in this review may require further investigation. Also unknown is whether the MYC2 protein is posttranslationally modified during JA signaling. The phosphorylation site identified in the MYC2 protein (Figure 2) along with earlier work implicating the importance of phosphorylation in JA-mediated wound signaling (Rojo et al., 1998) suggests that phosphorylation could be a process that affects the stability and the activity of MYC2. Although negative regulation of MYC2 transcript levels by the MKK3–MPK6 MAPK cascade has been reported (Takahashi et al., 2007), additional research is required to determine whether MYC2 activity is specifically altered through phosphorylation and possible relevance of such alterations in MYC2-mediated processes.

As is becoming increasingly evident, MYC2 controls the crosstalk between JA and nearly all the other hormone signaling pathways. The overlapping signaling pathways regulated by exogenous (e.g. light quality) and endogenous (e.g. the circadian clock and phytochrome) signals also require MYC2 function for successful integration of these signals into phytohormone pathways. Recent evidence implicates MYC2 even in ROS signaling modulated by the plasma membrane-located respiratory burst oxidase (NADPH oxidase) homologs RBOHD and RBOHF (Torres et al., 2002). JA-responsive expression of *VSP1*, *ANAC019*, and *ANAC055* positively regulated by MYC2 shows attenuation in *rbohD* and *rbohF* single mutants. However, *MYC2* transcript levels are similarly induced in these mutants and in the wild-type after MeJA treatment, suggesting that RBOHD and RBOHF act upstream from MYC2 and the ROS generated by these plasma membrane proteins is required for the expression of genes positively regulated by MYC2 (Maruta et al., 2011). It is likely that future research will reveal additional MYC2-regulated roles in the regulation of cross-communication between plant signaling pathways.

So far, the function MYC2 has been mainly studied in *Arabidopsis*. Emerging evidence from other dicots (e.g. tobacco and tomato) suggests that the MYC2 function is broadly conserved (Boter et al., 2004; Shoji and Hashimoto, 2011; Zhang et al., 2011, 2012). Putative MYC2 orthologs were found in rubber tree (*Hevea brasiliensis*) (Zhao et al., 2011). A recent study implicates two MYC2 orthologs, MaMYC2a and MaMYC2b, in the regulation of JA-induced chilling tolerance in banana (*Musa acuminate*) fruit. Interestingly, both MaMYC2a and MaMYC2b interact with the bHLH TF MaICE1 (Zhao et al., 2013). The *Arabidopsis* ortholog of this TF, ICE1, is a regulator of freezing tolerance and is predicted to interact with MYC2 (Chen et al., 2012b; see above). However, relatively little is known about the function of MYC2 orthologs/homologs in economically important monocot plants. A recent study in maize (*Zea mays*) implicated MYC7, a putative MYC2 ortholog, in systemic signaling activated in response to insect elicitors (Engelberth et al., 2012). The rice gene *RERJ1* encoding a wound-responsive bHLH TFs requires JA for its expression (Miyamoto et al., 2012). Another recently characterized bHLH protein in rice (*Oryza sativa*), OsbHLH148, has a role in abiotic stress tolerance (Seo et al., 2011). OsbHLH148 is not the closest homolog of MYC2 based on the amino-acid sequence similarities between these two proteins at the conserved bHLH region. However, the MeJA- and ABA-inducibility of *OsbHLH148*, the physical interactions observed between the OsbHLH148 protein, and the members of the OsJAZ family as well as the observation that *OsbHLH148* overexpressing plants show increased expression of JAZ encoding genes are all indicative of OsbHLH148 being a functional homolog of MYC2. A better understanding of JA signaling and the functions of MYC2 orthologs in economically important crop species would not only reveal additional unique roles, but also help develop new strategies for genetic manipulation of these plants for enhanced tolerance to environmental stresses.

NOTE ADDED IN PROOF

A recent paper by Withers et al. (2012) published after the acceptance of this review provides experimental evidence that the NLS located at the C-terminus of the MYC2 protein (Figure 2) is important for nuclear targeting of not only MYC2 but also for JAZ1 and JAZ9 repressors. This new finding showing MYC2's involvement in nuclear translocation of JAZ repressors represents another important signaling function executed by this master regulator.

SUPPLEMENTARY DATA

Supplementary Data are available at *Molecular Plant Online.*

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