A Rolling Stone Gathers No Moss, but Resistant Plants Must Gather Their MOSEs

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The detection of pathogenic microbes by plant resistance (R) proteins and the subsequent activation of R protein-mediated immunity constitute an important layer in the plant innate immune system. Most R genes encode proteins with nucleotide-binding (NB) and leucine-rich repeat (LRR) domains. The autoimmune mutant *suppressor of npr1, constitutive 1* (*snc1*), that constitutively activates resistance signaling, is a unique model used in our laboratory to dissect the details of TIR (Toll/Interleukin1 receptor)–NB-LRR, protein-mediated defense responses. Suppressor screens of *snc1* yielded 15 *modifier of snc1* (*mos*) complementation groups containing second-site mutations, and resulted in the identification of 13 novel MOS genes via either positional cloning or T-DNA tagging. Characterizations of the *mos* mutants have revealed important roles for transcriptional regulation, RNA processing, protein modifications, and nucleocytoplasmic trafficking in R protein-mediated immunity. The MOS genes have taught us a great deal about the complex mechanisms surrounding R protein activation. Future in-depth genetic and biochemical analyses will further enhance our knowledge of how R proteins are deliberately activated and how specific, targeted immunity is achieved in plants.

Plants have several means of defending themselves against microbial pathogens including bacteria, fungi, and viruses. They may possess a variety of physical barriers, such as a waxy epidermis and rigid cell walls, that help to protect against infection (Heath 2000). These defense systems largely constitute nonhost resistance. A plant is considered a “host” if it can be colonized by a given pathogen. Upon pathogen detection, multilayered defense responses are triggered in the plant to hinder the infection process (Dangl and Jones 2001).

The first layer of host resistance, termed PAMP-triggered immunity (PTI), is initiated by the recognition of conserved microbial features known either as pathogen- or microbial-associated molecular patterns (PAMPs or MAMPs), such as bacterial flagellin, by transmembrane receptors in plant cells (Boller and Felix 2009). This relatively weak resistance can be interfered with or suppressed by pathogen-specific effector molecules. These products are delivered into the host by pathogens, resulting in successful infection and thus disease. However, plants have evolved a stronger, rapidly elicited second layer of defense mediated by resistance (R) proteins. R proteins serve as immune receptors that recognize specific effector molecules, encoded by *Avirulence* (*Avr*) genes, through direct or indirect protein–protein interactions (Chisholm et al. 2006; Jones and Dangl 2006). Many R genes have been cloned during the past 20 years, the majority of which encode proteins containing a central nucleotide-binding (NB) domain and carboxy-terminal leucine-rich repeats (LRRs) (Ellis et al. 2000). These NB-LRR R proteins can be divided into two subclasses

based on whether their amino terminus contains a coiled-coil (CC) domain or a domain with homology to the Toll/Interleukin1 receptor (TIR). These two classes of NB-LRR proteins activate distinct downstream signaling pathways. Resistance mediated by TIR-NB-LRR R proteins tends to signal through the EDS1/PAD4/SAG101 complex (Enhanced Disease Susceptibility 1; Phytoalexin Deficient 4; Senescence-Associated Gene 101), whereas CC-NB-LRR R proteins usually activate resistance through the membrane-bound protein NDR1 (Nonrace Specific Disease Resistance 1) (Century et al. 1997; Aarts et al. 1998; Feys et al. 2005). Interestingly, some conserved CC-NB-LRR proteins such as ADRs have been found to act as signaling intermediates rather than as canonical recognition receptors (Peart et al. 2005; Bonardi et al. 2011; Collier et al. 2011).

R protein-mediated immunity is characterized by two major events: local programmed cell death at the infection site, referred to as the hypersensitive response (HR) that is thought to prevent the spread of pathogens, and systemic acquired resistance (SAR), which confers long-lasting broad range enhanced resistance (Durrant and Dong 2004). HR is accompanied by a series of physiological changes including altered ion fluxes, the accumulation of the defense hormone salicylic acid (SA), the induction of *pathogenesis-related* (*PR*) genes, and an oxidative burst (Hammond-Kosack and Jones 1996). Genetic analysis of *Arabidopsis* mutants with deficiencies in SA-induced *PR* gene expression led to the identification and cloning of *NPR1* (*Non-Expressor of PR Genes 1*), which is a positive regulator of SAR thought to function

downstream from SA accumulation triggered by R protein activation (Cao et al. 1997).

A subsequent genetic screen undertaken to identify suppressors of *npr1* led to the isolation of a unique gain-of-function mutant, *snc1* (*suppressor of npr1-1, constitutive 1*), which encodes a TIR-NB-LRR protein (Li et al. 2001). In *snc1*, a glutamic acid to lysine substitution in the linker region between the NB and LRR domains results in constitutive activation of defense, without pathogen perception. The autoimmune phenotypes of *snc1* include dwarfed stature, increased levels of SA, constitutive expression of *PR* genes, and increased resistance against virulent pathogens such as the bacteria *Pseudomonas syringae* pv. *maculicola* (*P.s.m.*) ES4326 and the oomycete *Hyaloperonospora arabidopsidis* (*H.a.*) Noco2 (Zhang et al. 2003). As with most TIR-type NB-LRR proteins, *snc1* signals through PAD4 and EDS1.

SNC1 resides in the *RPP4* cluster on chromosome 4 in the Columbia (Col) ecotype. *SNC1* is highly homologous to *RPP4* and *RPP5*, with >70% similarity at the amino acid level. The majority of the sequence dissimilarity occurs within the LRR domain, because the TIR-NB domain of *SNC1* is almost identical to that of *RPP4* and *RPP5*. Due to its presence in certain ecotypes, such as Col, but absence from other ecotypes, including Landsberg *erecta* (*Ler*) and Wassdilewskija (*Ws*), we believe that *SNC1* is most likely to be a bona fide *R* gene. In support of that, loss-of-function *snc1* alleles do not show enhanced disease susceptibility as *adr* triple mutants do (Bonardi et al. 2011). However, the cognate Avr protein for *SNC1* remains to be discovered.

Because the *snc1* mutation activates resistance signaling pathways without producing HR lesions, this unique autoimmune mutant is a useful tool for dissecting signaling events surrounding TIR-NB-LRR activation. Multiple mutagenesis strategies have been used in *snc1* suppressor screens, yielding a number of *modifier of snc1* (*mos*) mutants. We originally hypothesized that the activated *snc1* R protein needs sophisticated downstream signaling components such as EDS1 and PAD4 to transduce the “danger alarm” to induce defense outputs. The suppressor screen should yield mostly positive regulators of the signaling pathway.

In the primary screen, M2 generations of ethyl methanesulfonate (EMS), T-DNA, or fast-neutron mutagenized *snc1* and *snc1 npr1* populations were screened for loss of *snc1* dwarf morphology under normal lab growth conditions (i.e., 22°C, 16-h day/8-h night, ~50% humidity). To confirm that mutants isolated from the primary screen are indeed *snc1* suppressors and are involved in plant immunity, defense-related phenotypes including *PR* gene expression, endogenous SA levels, and resistance to *P.s.m.* ES4326 and *H.a.* Noco2 were assessed in M3 populations as part of the secondary screen. Consistent with the prediction, the *snc1 mos* mutants show wild-type-like morphology and have decreased levels of all examined defense outputs. In total, 15 independent complementation groups of mutants showed varying degrees of suppression of the *snc1* autoimmune phenotypes.

During the secondary screen, one of the challenges we faced was to identify and discard mutants containing intragenic *snc1* mutations, which constituted the majority of the mutants isolated from the primary screen. Fortunately, loss-of-function *snc1* mutations typically result in a dominant wild-type-like morphological phenotype when heterozygous with the gain-of-function *snc1* mutation. Using this criterion, we were able to focus on <10% of the recessive mutants carrying mutations in second-site genes.

Positional cloning was used to clone 11 of the 13 novel *MOS* genes. To facilitate mapping, *snc1*, originally in the Col background, was introgressed into *Ler* through six backcrosses. Crosses between *snc1 mos* mutants and the *Ler-snc1* line were generated. The F₁ plants, which displayed *snc1*-like morphology owing to the recessive nature of the *mos* genes, were allowed to self-fertilize to generate a segregating F₂ population suitable for conducting linkage analysis between the suppression of *snc1* morphology and molecular markers (Zhang and Li 2005). Typically, a population of 600–1000 F₂ plants would enable us to narrow the region containing each mutation to <100 kb, and genes within that region were directly sequenced to identify the putative molecular lesions. Once the mutations were identified, *MOS* gene cloning was confirmed by transgenic complementation and allelism tests if alternate T-DNA alleles were available from the *Arabidopsis* Biological Resource Center (ABRC).

As expected, several mutant alleles of *PAD4* were identified. To date, 13 novel *MOS* genes have been cloned using positional cloning (11) and T-DNA tagging (2) approaches (Table 1). These encode proteins involved in RNA processing, nucleocytoplasmic trafficking, protein modification, and epigenetic control of gene expression. The diverse *MOS* functions suggest that the activation of R protein-mediated resistance is highly complex (Palma et al. 2005, 2007; Zhang and Li 2005; Zhang et al. 2005; Goritschnig et al. 2007; Wiermer et al. 2007; Goritschnig et al. 2008; Cheng et al. 2009; Germain et al. 2010; Li et al. 2010; Xu et al. 2011, 2012).

SECTION THEMES ON *MOS* GENES

Regulators of *SNC1* Gene Expression Levels: *MOS1* and *MOS9*

The *snc1* mutant displays morphological dwarfism together with constitutive defense activation, suggesting that maintaining R protein-mediated defense requires sacrifices to plant fitness. Accordingly, *R* gene expression must be tightly controlled under normal conditions. However, the regulatory mechanisms of *R* gene transcriptional control are largely unknown. In addition to conventional regulation by transcription factors, epigenetic regulation via chromatin or histone modification has emerged as being important for fine-tuning transcriptional control. For example, expression of the TIR-NB-LRR-encoding gene *LAZ5* requires trimethylation of H3K36 (Histone 3, lysine 36) by the histone lysine methyltransferase SDG8 to maintain a transcriptionally active chromatin state (Palma et al. 2010).

Table 1. A summary of *MOS* genes that have been characterized

Gene name	Code	Mutagen	Suppression level	Single mutant EDS (Y/N)	Type of mutation	Protein information	Protein location
<i>MOS1</i>	At4g24680	FN	Complete	N	8-bp deletion in <i>mos1-1</i>	Conserved BAT2 domain	Nucleus
<i>MOS2</i>	At1g33520	FN	Partial	Y	2-bp insertion in <i>mos2-1</i>	One G patch; two KOW domains	Nucleus
<i>MOS3</i>	At1g80680	FN	Complete	Y	Point mutation in <i>mos3-1</i>	AtNup96, a nucleoporin	Nuclear envelope
<i>MOS4</i>	At3g18165	FN	Complete	Y	2.2-kb insertion in <i>mos4-1</i>	Homologous to human BCAS2; part of MAC	Nucleus
<i>MOS5</i>	At2g30110	FN	Partial	Y	15-bp deletion in exon	AtUBA1	Everywhere
<i>MOS6</i>	At4g02150	FN	Partial	Y	5.3-kb chromosomal rearrangement in <i>mos6-1</i>	Importin	Nucleus
<i>MOS7</i>	At5g05680	FN	Complete	Y (oomycete)	12-bp deletion in <i>mos7-1</i>	Nup88; null allele lethal	Nuclear envelope
<i>MOS8</i>	At5g40280	FN	Partial	Y	Point mutation affecting start codon	β subunit of protein farnesyltransferase	Unknown
<i>MOS9</i>	At1g12530	FN	Partial	N	Deletion in <i>mos9-1</i>	Unknown	Nucleus
<i>MOS10</i>	At1g80490	T-DNA	Partial	N	Deletion	AtTPR1, a transcriptional repressor; redundant with TPR4 and TPL	Nucleus
<i>MOS11</i>	At5g02770	T-DNA	Partial	N	T-DNA insertion in 5' UTR	CIP29homolog	Nucleus
<i>MOS12</i>	At2g26430	EMS	Complete	Y	G to A point mutation at exon–intron boundary	Cyclin L homolog; null allele lethal	Nucleus
<i>MOS14</i>	At5g62600	EMS	Complete	Y	G to A point mutation at exon–intron boundary	TRN-SR, an SR protein transporter	Nucleus

EDS: enhanced disease susceptibility; FN: fast neutron; MAC: MOS4-associated complex.

The identification of *MOS1* and *MOS9* has provided insights into the regulatory mechanisms of TIR-NB-LRR-encoding *R* gene expression. As with other *mos* mutants, loss of either *MOS1* or *MOS9* function suppresses all *snc1*-related phenotypes. *MOS1* encodes a protein containing an HLA-B ASSOCIATED TRANSCRIPT 2 (BAT2) domain that is conserved in both plants and animals (Li et al. 2010). Although an alteration of DNA methylation in a region upstream of *SNC1* is observed in the *mos1* mutant, it is not correlated with a repression of *snc1* expression level; thus, *MOS1* likely does not function directly in DNA methylation. Furthermore, transgenic *snc1* expression is not altered in *mos1*, indicating that *MOS1* may regulate *SNC1* expression at its specific chromosomal location. Interestingly, the repression of *snc1* expression level can be mitigated by introducing *ddm1* (*DECREASE IN DNA METHYLATION 1*), suggesting that *MOS1* and *DDM1* may function antagonistically to regulate the expression of *SNC1* at the chromatin level.

MOS9 encodes a plant-specific protein of unknown function (Y Cheng and X Li, unpubl.). In the loss-of-function *mos9* mutant, the expression levels of *SNC1* and another TIR-NB-LRR-encoding *R* gene, *RPP4*, are reduced. Immunoprecipitation of *MOS9* followed by mass spectrum analysis identified ATXR7 (*ARABIDOPSIS TRITHORAX-RELATED 7*) as a *MOS9*-associated protein. ATXR7 is a SET domain-containing H3K4 (Histone 3, Lysine 4) methylase required for the proper transcriptional activation of *FLC* (*FLOWERING LOCUS C*) via bulk methylation (Tamada et al. 2009). Identification of ATXR7 as a protein associated with *MOS9* suggests that *MOS9* likely regulates *R* gene transcription through H3K4me3 chromatin modification.

Components of the RNA Processing Machinery: *MOS2*, *MOS4*, and *MOS12*

To ensure appropriate functionality, stability, and localization, nascent pre-mRNA (messenger RNA) transcripts are subject to a number of processing steps including 5' capping, 3' polyadenylation, and splicing, followed by nuclear export. From our *MOS* screens, three genes were identified as important elements in RNA processing.

MOS2 is required for both CC- and TIR-NB-LRR *R* protein-mediated resistance (Zhang et al. 2005) and is also required for basal resistance against *P.s.m.* ES4326. These results suggest that *MOS2* acts as a point of convergence for a number of immune signaling pathways.

MOS2 is a nuclear protein containing one G patch and two KOW motifs that are conserved among the *MOS2* homologs in higher plants and animals. The glycine-rich G-patch motif is often found proximate to RS and RGG repeats, which have been implicated in nonspecific protein–RNA interactions (Aravind and Koonin 1999). Similarly, the KOW motif from the bacterial elongation factor NusG has shown nucleic acid-binding activity and shares structural homology with the tudor protein–protein interaction motif (Steiner et al. 2002). Whereas *MOS2* has not been experimentally shown to bind RNA, the human *MOS2* homolog GPKOW binds RNA in a manner dependent on protein kinase A (Aksaas et al. 2011). Furthermore, the remote yeast homolog SPP2 is an essential protein required for the first RNA cleavage step in pre-mRNA splicing. The G-patch domain of SPP2 associates the Prp2, an RNA-dependent ATPase that activates the spliceosome (Roy et al. 1995; Silverman et al. 2004; Yeh et al. 2011). Therefore, *MOS2* is predicted to bind RNA, appears to function in splicing, and may also

interact with other proteins via its KOW motif. However, the precise role of MOS2 in RNA processing, particularly within an immunity context, remains unclear. Interestingly, the involvement of the yeast MOS2 homolog in pre-mRNA splicing provides evidence that a connection may exist between the roles of MOS2 and MOS4 in regulating plant immunity.

As with MOS2, MOS4 is a nuclear protein that is required for basal resistance against *P.s.m.* ES4326 as well as for both TIR- and CC-NB-LRR-type R protein-mediated resistance (Palma et al. 2007). Along with 23 other proteins, it forms a highly conserved spliceosome-associated complex known as the MOS4-associated complex (MAC) in *Arabidopsis* (Monaghan et al. 2009). All examined MAC component single mutants are viable but display pleiotropic defects, whereas all double mutant combinations are lethal (Nemeth et al. 1998; Palma et al. 2007; Monaghan et al. 2009, 2010). This indicates that whereas individual MAC components may be involved in regulating a number of different biological processes, the complex as a whole is required for some essential function, such as general mRNA splicing.

Yeast and human orthologous complexes have been implicated in spliceosome assembly and pre-mRNA splicing (Tarn et al. 1993; Ajuh et al. 2000; Ohi et al. 2002; Deckert et al. 2006), and it is expected that the MAC has a similar role in plants owing to the conserved nature of the complex. Several MAC components, including MOS4, were recently shown to be necessary for the proper splicing of *RPS4* and *SNC1* (Xu et al. 2012). It is tempting to hypothesize that defense-related gene transcripts may be differentially processed upon pathogen detection through modulation of the MAC.

Although MOS2 has not been shown to directly associate with the MAC, human and yeast homologs of MOS2 have been implicated as components of the conserved spliceosome-associated complex (Roy et al. 1995; Besonov et al. 2010; Aksaas et al. 2011). Additionally, MOS2 has been shown to be required for proper splicing of *SNC1* (S Xu and Y Zhang, unpubl.). This provides further support that MOS2 is also involved in RNA processing, possibly in conjunction with the MAC.

MOS12 is required for basal resistance against *P.s.m.* ES4326 as well as for resistance mediated by a subset of R proteins, primarily those belonging to the TIR-NB-LRR class (Xu et al. 2012). *MOS12* encodes a nuclear arginine-rich protein with two cyclin domains at the amino terminus. Its closest homolog is human cyclin L, which is predicted to be involved in mRNA splicing owing to its association with splicing factors and ability to stimulate splicing in vitro (Dickinson et al. 2002; de Graaf et al. 2004).

The *mos12* allele isolated from *MOS* screens (*mos12-1*) contains a point mutation at an intron–exon splice junction, which causes a reading frame shift, resulting in a truncated protein (Xu et al. 2012). However, the truncated protein is likely still partially functional because the null *mos12-2* T-DNA insertion allele is lethal, indicating that this gene has an essential role in plant growth and development.

In *mos12-1* plants, the splicing patterns of both *SNC1* and *RPS4* are altered from those observed in wild-type plants (Xu et al. 2012). In addition, MOS12 coimmunoprecipitates with MOS4. Together, these results indicate that MOS12 has a critical role in the splicing of R gene transcripts, likely in association with the MAC through the spliceosome.

Plant defense responses may be regulated in part through alternative splicing of R gene transcripts, because pathogen detection has been shown to elicit the production of splice variants of a number of TIR-NB-LRR-encoding genes including tobacco *N* and *Arabidopsis* *RPS4*, among others (Dinesh-Kumar and Baker 2000; Zhang and Gassmann 2003). In tobacco, transcripts of the R gene *N* are alternatively spliced following pathogen attack, and a specific ratio of full-length and truncated N proteins is thought to be required for complete resistance against tobacco mosaic virus because neither splice variant is able to individually induce defense response outputs (Dinesh-Kumar and Baker 2000). Similarly, alternative splicing of *RPS4* is induced in *Arabidopsis* following pathogen detection, and alternatively spliced transcripts are required for complete *RPS4*-mediated immunity (Zhang and Gassmann 2003). Increased expression of the *RPS4* transcript is induced by the recognition of avrRps4, HopA1, or avrRpt2 effector molecules, of which only avrRps4 is specifically recognized by RPS4 (Zhang and Gassmann 2007). Additionally, detection of avrRps4 resulted in the altered splicing of not only *RPS4* but also of two other *Arabidopsis* genes known to have alternatively spliced forms; only one of these is thought to potentially function in defense response. Therefore, it has been proposed that increased TIR-NB-LRR transcript production and alternative splicing may constitute a general response used to prime plants for resistance. Although alternative splicing of R genes has been predominantly observed for TIR-NB-LRR transcripts, there are reports of CC-NB-LRR gene transcript alternative splicing as well (Halterman et al. 2003; Peart et al. 2005).

Nuclear Proteins Important for mRNA Export: The Nup107-160 Complex and MOS11

Cellular compartmentalization in eukaryotic cells requires that processed transcripts be delivered into the cytoplasm before translation can occur. This provides an additional tier of regulation by controlling the nuclear export of mature mRNA molecules. Export of transcripts that are successfully processed requires RNA export proteins such as nuclear export factors, nucleoporins, and RNA chaperones. Although much insight has been gained using human and yeast models, RNA nucleocytoplasmic trafficking is still poorly understood in plants.

Common features exist in the *mos3* and *mos11* mutants, because they both suppress the constitutive autoimmune phenotypes of *snc1* (Zhang and Li 2005; Germain et al. 2010). In addition, the *mos3* single mutant shows enhanced disease susceptibility to both virulent and avirulent pathogens, suggesting that MOS3 functions in both

basal and R protein-mediated defense. However, such increased susceptibility was not observed in the *mos11* single mutant. In situ hybridization of total mRNA revealed a dramatic accumulation of transcripts in the nucleus of each mutant, suggesting that MOS3 and MOS11 are both required for successful mRNA export (Parry et al. 2006; Germain et al. 2010).

MOS3 localizes to the nuclear rim whereas MOS11 is present in the nuclear matrix, suggesting that MOS11 may function before MOS3 in the mRNA export process (Zhang and Li 2005; Germain et al. 2010). *MOS11* encodes a homolog of human CIP29, an RNA cochaperone enhancing the activity of RNA helicase DDX39 (Sugiura et al. 2007; Dufu et al. 2010). MOS11 may function as part of a similar complex during the mRNA export process in plants.

MOS3 is homologous to nucleoporin (Nup) 96 in mammals and Nup145 in yeast, both of which have been reported to be involved in mRNA export (Fabre et al. 1994; Vasu et al. 2001). Nup96 functions as part of the Nup107-160 nuclear pore subcomplex. In mice, the loss-of-function *nup96* allele is lethal when homozygous and the immune systems of heterozygotes are severely impaired, indicating that Nup96 functions in both innate and adaptive mammalian immunity (Faria et al. 2006). MOS3 is thought to function as part of a homologous complex in *Arabidopsis*, and other putative complex components including Nup160 and Seh1 were recently shown to be required for basal and TIR-NB-LRR-mediated resistance (Wiermer et al. 2012). Although it is uncertain how a general defect in nonspecific mRNA export impairs R protein-mediated immunity without serious developmental consequences, one possibility is that plants have evolved to be more resilient, and loss of only one component of the Nup107-160 complex does not lead to lethality. However, the double mutant of *nup96 nup160* is seedling lethal (Parry et al. 2006).

Components Involved in Nucleocytoplasmic Protein Trafficking: MOS6, MOS7, and MOS14

The *mos6* mutant alleles were identified in suppressor screens either in *snc1* or *snc1 npr1* backgrounds (Palma et al. 2005). In all cases, *mos6* alleles partially suppress the autoimmune phenotypes of *snc1*. Interestingly, the *mos6* single mutant shows enhanced disease susceptibility to *H.a. Noco2* but not to *P.s.m.* ES4326, indicating that MOS6 may have a specific role in basal defense against oomycete infection. Positional cloning of *MOS6* showed that it encodes importin α 3. The MOS6 protein has the typical features of importin α proteins including an importin β -binding domain and NLS-binding pockets. Green fluorescent protein (GFP) localization of MOS6 showed that it is concentrated in the nucleus, which supports the idea that it is a functional importin α (Palma et al. 2005). Within the *Arabidopsis* genome, eight genes encode homologs of importin α , including *MOS6*. This large number of importin homologs in *Arabidopsis* is unsurprising, given the essential role of protein import

in every aspect of plant growth and development. Whether a subset of these importin α homologs is specifically involved in plant defense response is not known. Because all importin α proteins bind NLS, there are likely protein–protein interaction domains defining specificity.

Besides its involvement in *snc1*-mediated defense, MOS7 has also been suggested to have roles in basal defense and defense mediated by other R proteins. Furthermore, SAR is compromised in the *mos7* single mutant, because pretreatment of *mos7* plants with an avirulent bacterial pathogen failed to trigger subsequent immunity in distal leaves (Cheng et al. 2009). *MOS7* encodes a protein with homology to Nup88 in animals, which is involved in nuclear protein export (Uv et al. 2000). MOS7 localizes to the nuclear rim, indicating its potential role as a nucleoporin in *Arabidopsis*. Intriguingly, the nuclear accumulations of NPR1, EDS1, and SNC1 are reduced in the *mos7-1* single mutant as compared with the wild-type, whereas the nuclear distributions of HDA19, CDC5, and TGA2 remain unchanged (Cheng et al. 2009). This suggests that there is specificity in the protein export pathways affected by the *mos7-1* mutation. However, because MOS7 is a single-copy gene in the *Arabidopsis* genome and the *mos7-2* null T-DNA insertion allele is lethal, wild-type MOS7 is likely required for general nuclear protein retention. Further work is required to determine how the *mos7-1* mutation leads to the specific enhancement of nuclear export activity of immunity-related proteins such as SNC1, EDS1, and NPR1.

MOS14 is a required intermediate in both basal resistance and some TIR-NB-LRR R protein-mediated resistance signaling pathways (Xu et al. 2011). It is a single copy gene in *Arabidopsis*, encoding a nuclear protein with homology with metazoan transportin-SR (TRN-SR) proteins, which are nuclear import receptors. TRN-SR proteins belong to the importin- β superfamily, members of which mediate the import of protein cargo through the nuclear pore complex (NPC) upon recognition of a nuclear localization signal (NLS). TRN-SR proteins specifically transport serine–arginine-rich (SR) proteins, that function in both constitutive and alternative splicing through their roles in pre-mRNA splice site recognition and spliceosome assembly (Long and Caceres 2009).

The MOS14 protein was shown to interact with four different SR proteins through its carboxyl terminus and AtRAN1, which is required for release of the cargo into the nucleus through its amino terminus (Xu et al. 2011). In the homozygous *mos14-1* mutant, nuclear localization of SR proteins is impaired. In keeping with this mislocalization of known splicing factors, the splicing patterns of *SNC1* and *RPS4* are altered in *mos14-1* plants, and resistance mediated by these proteins is attenuated.

Studies of MOS6, MOS7, and MOS14 have revealed the importance of nucleocytoplasmic protein trafficking in the regulation of plant defense. In addition to the mRNA export process discussed previously, fine-tuned nuclear import and export of defense regulators seem to have a key role in mounting effective immunity in plants.

Transcriptional Corepression with SNC1: MOS10 (TPR1)

MOS10 encodes a nuclear protein with high sequence similarity to *TOPLESS* (*TPL*) (Zhu et al. 2010), a transcriptional corepressor that functions during embryogenesis in an auxin-dependent manner (Szemenyei et al. 2008). As such, *MOS10* was renamed *TOPLESS RELATED 1* (*TPR1*). As with *TPL*, *TPR1* is a transcriptional corepressor, a unique biological function among the identified *MOS* proteins.

Both *TPR1* and *TPL* are required for basal immunity as well as resistance mediated by a number of TIR-NB-LRR-type R proteins (Zhu et al. 2010). Overexpression of *TPR1* results in the constitutive activation of defense phenotypes similar to those observed in the *snc1* mutant including increased SA accumulation, constitutive *PR* gene expression, and enhanced resistance to *H.a. Noco2*. These responses in the *TPR1* overexpression lines require *EDS1*, *PAD4*, and *SNC1*. Coimmunoprecipitation experiments showed that *TPR1* and *SNC1* associate with one another in planta, likely through the TIR domain of *SNC1*.

The homozygous *tpl* mutant displays phenotypes similar to those observed in *histone deacetylase 19* (*hda19*) including apical shoot defects (Long et al. 2006). Additionally, the *hda19* single mutant shows compromised pathogen resistance (Kim et al. 2008). Coimmunoprecipitation experiments indicate that *TPR1* associates with *HDA19* in vivo (Zhu et al. 2010). Histone deacetylases remove acetyl groups from a histone lysine residue, thereby enhancing DNA condensing, which, in turn, inhibits transcription. *TPR1* has been shown to associate with the promoters of *DEFENSE NO DEATH 1* (*DND1*) and *DND2*, two known negative regulators of immunity, and may act together with *HDA19* to regulate their transcription. *SNC1* and other R proteins may activate downstream defense responses through the regulation of the transcriptional repression activity of *TPR1*.

Protein-Modifying Enzymes: MOS5 and MOS8

In most eukaryotes, posttranslational modifications (PTMs) modulate protein function by influencing their activity, stability, and localization. PTMs are needed to regulate a diverse range of cellular functions. Increasing evidence indicates that PTMs, such as ubiquitylation and phosphorylation, have an important role in plant defense signaling.

The identification of *MOS5* and *MOS8* indicates that PTMs are crucial in regulating R protein activation. *MOS5* encodes one of two ubiquitin-activating enzymes (E1) in *Arabidopsis* (Goritschnig et al. 2007). Along with E2 (ubiquitin-conjugating enzyme) and E3 (ubiquitin ligase) enzymes, E1s are involved in labeling protein substrates with ubiquitin moieties, typically to mark a substrate for degradation by the 26S proteasome. The loss of *MOS5* function partially suppresses *snc1* phenotypes and leads to both impaired basal and R protein-mediated defense activity. The single mutant of the other

Arabidopsis E1 enzyme, *uba2*, displays no obvious phenotypic defects, but the *mos5 uba2* double mutant is lethal, indicating that a large degree of redundancy exists between these two E1 enzymes.

The *mos5* mutant contains a molecular lesion in the putative ubiquitin-fold domain, which likely disrupts the ubiquitylation process. The enhanced susceptibility phenotypes observed in the *mos5* mutant may result from the increased stability of negative defense regulators, the degradation of which might be essential in *snc1*-mediated defense resistance. Alternatively, the *mos5* mutation may disrupt the function of positive defense regulators, which may require mono-ubiquitination for activation. Recent work has shown that the F-box protein *CPR1*, which belongs to the SKP1-CULLIN1-F-box (SCF) E3 complex, targets *SNC1* and other NB-LRRs for degradation, highlighting the importance of ubiquitylation in regulating R protein levels and preventing autoimmunity (Cheng et al. 2011). Surprisingly, whereas *mos5* suppresses the dwarf phenotype of *snc1*, it enhances the stunted growth morphology observed in *cpr1-2* (Gou et al. 2012). The complex *mos5* phenotype is likely a result of the mutant allele's impact on multiple E3 enzyme activities (Cheng and Li 2012).

Other PTMs that modify protein localization, solubility, and protein-protein interactions are also required in defense signal transduction. The common lipid modification, prenylation, involves the covalent binding of hydrophobic farnesyl- or geranylgeranyl-diphosphate moieties to the target proteins, likely facilitating their binding to cellular membranes (Galichet and Grissem 2003). *mos8* is an allele of *ERA1* (*ENHANCED RESPONSE TO ABSCISIC ACID1*), which encodes the β subunit of farnesyl-transferase (Goritschnig et al. 2008). As with other *eral* alleles, *mos8* displays enhanced susceptibility to *P.s.m.* ES4326 and *H.a. Noco2*, implying a role of farnesylation in basal immunity. It also shows impaired defense responses mediated by several R proteins. Furthermore, epistatic analyses using *eral* and several abscisic acid (ABA) biosynthesis mutants indicates that enhanced susceptibility of *eral* is only partially dependent on ABA. The *eral npr1* double mutant displays enhanced *eral* phenotypes, indicating that *ERA1* functions in an *NPR1*-independent pathway. Even though the target proteins modified by *ERA1* are currently unknown, lipid modification is likely playing an important part in disease resistance signaling by targeting substrate proteins to cellular membranes and altering their activities.

CONCLUSIONS

The results of the *MOS* screens were somewhat surprising in that they primarily resulted in the identification of novel factors regulating transcription, RNA processing, nucleocytoplasmic trafficking, localization, and activity of R genes and their encoded products. We propose a model that brings together these seemingly disparate functions within a resistance signaling context, centering on R protein activation (Fig. 1). Our model suggests that

Figure 1. A model depicting the involvement of the MOS proteins in R protein-mediated defense signaling pathways in *Arabidopsis*, using SNC1 as an example of the journey of TIR-NB-LRR proteins. 1. At the chromosomal level, MOS1, ATXR7, and MOS9 up-regulate the transcription of *SNC1* through chromatin remodeling. 2. MOS2, MOS4, and MOS12 are required for proper splicing of the transcripts of *SNC1*. 3. The Nup107-160 complex and MOS11 have key roles in the export of total mRNA (including mature mRNA of *SNC1*), which is required for effective defense. 4. MOS5 is an E1 ubiquitin-activating enzyme, an essential component of the ubiquitination cascade, required for the regulation of defense signaling components. As an example, the SCF^{CPR1} E3 ubiquitin ligase complex targets SNC1 for degradation, which prevents autoimmunity caused by overaccumulation of R proteins. MOS8 positively regulates plant defense, possibly through prenylation, which affects the targeting of defense regulators. 5. MOS6 and MOS7 are involved in the nucleocytoplasmic shuttling of defense signaling molecules such as SNC1, EDS1, and NPR1. As with RPS4, EDS1 is probably required for the nuclear localization and activation of SNC1 upon recognition of its corresponding effector (Bhattacharjee et al. 2011; Heidrich et al. 2011). MOS14 is required for the nuclear import of splicing factors, which may affect defense regulator RNA processing. 6. MOS10 activates the SNC1-mediated defense through transcriptional repression of negative regulators of defense such as *DND1* and *DND2*.

R protein-mediated signaling may not consist of a long, linear signaling pathway possessing numerous intermediates as we imagined earlier. Rather, the primary regulatory steps exist at the *R* gene and R protein processing levels. Collectively, characterized MOS genes provide new insights into the complex regulatory mechanisms governing R protein-mediated immunity.

In the absence of pathogens, low *R* gene expression levels maintain a small amount of R proteins that putatively act as a surveillance system, protecting against pathogen attack. Upon pathogen detection, a number of factors including MOS1, ATXR7, and MOS9 likely alter chromatin structure or histone codes to up-regulate *R* gene transcription, thus enhancing pathogen detection capabilities and amplifying defense response signaling (Li et al. 2010; Y Cheng and X Li, unpubl.).

The processing of *R* gene transcripts is another regulatory node. MOS2, MOS4, MOS12, and MOS14 are all

required for correct *R* gene splicing (Xu et al. 2011, 2012; F Xu and Y Zhang, unpubl.). Following pathogen detection, these proteins may aid in recruiting the spliceosome preferentially to *R* gene transcripts to increase the speed, specificity, and strength of defense response activation. Alternatively, these proteins may have a role in *R* gene transcript alternative splicing, which is thought to provide specificity in the type and strength of immune response activated.

After splicing, transcripts must be exported to the cytosol to be translated. The Nup107-160 complex, which includes MOS3, functions in the same mRNA export pathway as MOS11 (Zhang and Li 2005; Germain et al. 2010; Wiermer et al. 2012). The mRNA export process could be another regulatory step modulating the final defense response outputs from *R* genes.

After translation in the cytosol, protein activity and localization may be altered by PTMs. MOS5 functions

as an essential part of the ubiquitination pathway, which results in the addition of ubiquitin moieties to target proteins (Goritschnig et al. 2007). This may mark negative defense regulators for proteasomal degradation or, alternatively, activate positive regulators. MOS5 likely has a general role in ubiquitination. MOS8 is required for prenylation (Goritschnig et al. 2008), a type of PTM that regulates protein membrane targeting (Resh 2006). MOS8 may direct defense regulators to their correct locations, thereby allowing signal transduction to proceed, although its targets have not yet been identified.

Following protein synthesis and modifications, many defense regulators are transported back to the nucleus in order for defense activation to occur. MOS6 and MOS7 are likely involved in the nuclear import and retention of defense-related proteins, although the degree of specificity in the activity of these proteins is unclear (Palma et al. 2005; Cheng et al. 2009). MOS14 is required for the nuclear import of SR proteins, most of which are splicing factors (Xu et al. 2011). Although MOS14 is required for precise *R* gene splicing, specificity has not been shown. Thus, *R* protein-mediated immunity may also be regulated by factors involved in nuclear import and export of proteins. These events affect the nuclear retention of key defense regulators and in turn determine the final levels of defense outputs.

MOS10/TPR1 is unique among the MOS proteins. It represses the transcription of known negative regulators of defense and associates with SNC1 in the nucleus, likely as part of a complex (Zhu et al. 2010). The association of SNC1 with MOS10/TPR1 appears to be required for the strong and rapid repression of negative defense regulators to mount an effective defense response.

During the past decade, studies of the *MOS* genes in our laboratory have provided some insights into the molecular details surrounding *R* protein-mediated immunity. However, the full picture of the regulation of NB-LRR *R* genes and their encoded products has not yet emerged. There are several key questions in our field that have yet to be answered. How are NB-LRR genes and their protein products activated upon pathogen detection or during feed-back up-regulation? How is the induction of *R* gene expression regulated to ensure sufficient production of *R* proteins while preventing autoimmunity? What is the link between local *R* protein activation and SAR? Why are many TIR-NB-LRR *R* genes temperature sensitive, whereas CC-NB-LRR *R* genes are not? Why are many TIR-NB-LRR *R* genes alternatively spliced, whereas most CC-NB-LRR *R* genes do not even contain introns? How is mRNA splicing specifically regulated during defense? Why do monocots not possess TIR-NB-LRRs at all yet maintain EDS1 and PAD4? What are the precise molecular functions of PAD4, EDS1, and NDR1, the major signaling intermediates of TIR- and CC-NB-LRR-mediated pathways, respectively?

We hope that through the efforts of our generation of molecular plant pathology researchers, we will be able to answer at least some of these fundamental questions in the near future. Our laboratory is currently undertaking a number of other genetic screens and more detailed

biochemical analyses on SNC1 and MOSes to explore some of the above questions in greater detail. The improved next-generation sequencing strategies and biochemical approaches guarantee an impending revolution in molecular studies of plant biology.

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