

# Induced Disease Resistance Signaling in Plants

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## ABSTRACT

To protect themselves from disease, plants have evolved sophisticated inducible defense mechanisms in which the signal molecules salicylic acid, jasmonic acid and ethylene often play crucial roles. Elucidation of signaling pathways controlling induced disease resistance is a major objective in research on plant-pathogen interactions. The capacity of a plant to develop a broad-spectrum, systemic acquired resistance (SAR) after primary infection with a necrotizing pathogen is well known and its signal transduction pathway extensively studied. Plants of which the roots have been colonized by specific strains of non-pathogenic fluorescent *Pseudomonas* spp. develop a phenotypically similar form of protection that is called rhizobacteria-mediated induced systemic resistance (ISR). In contrast to pathogen-induced SAR, which is regulated by salicylic acid, rhizobacteria-mediated ISR is controlled by a signaling pathway in which the phytohormones jasmonic acid and ethylene play key roles. In the past decade, the model plant species *Arabidopsis thaliana* has been extensively explored to study the molecular basis of systemically induced resistance. Here we review the current knowledge on induced disease resistance signaling in plants.

## 1. PLANT DISEASE RESISTANCE

### Non-host, basal and *R*-gene mediated resistance

Plants are sessile organisms, incapable of fleeing from possibly harmful organisms. In order to defend themselves against pathogen attack, plants possess a range of constitutive and inducible resistance mechanisms. The most effective type is non-host resistance. This non-host resistance is expressed when a plant comes into contact with a pathogen which is incapable of provoking any disease in this plant (Heath 2002). In the absence of non-host resistance, the plant is susceptible. However, even susceptible plants are capable of reacting in a way that may slow down growth of the pathogen. The presence of such basal resistance was evidenced in *Arabidopsis* by the isolation of enhanced disease susceptibility (*eds*) mutants. These mutants showed increased susceptibility to moderately virulent pathogens such as *Pseudomonas syringae* (Glazebrook *et al.* 1996, Rogers and Ausubel 1997). Basal resistance is often dependent on the action of one or more of the plant hormones jasmonic acid (JA), ethylene (ET) and salicylic acid (SA). Upon attack, the levels of these hormones are usually enhanced. Such enhancement depends on the attacker that is trying to invade the plant, and each of the hormones act in the resistance against a specific set of pathogens. For instance, basal resistance against the oomyceteous pathogen *Hyaloperonospora parasitica* or the viral pathogen turnip crinkle virus was reduced in *Arabidopsis* mutants affected in pathogen-induced biosynthesis of SA. In contrast, it was not reduced in mutants impaired in JA- or ET-signaling (Delaney *et al.* 1994, Thomma *et al.* 1998, Nawrath and Métraux 1999, Kachroo *et al.* 2000, Ton *et al.* 2002c). Conversely, JA- and ET-signaling mutants showed enhanced susceptibility to the fungal pathogens *Alternaria brassicicola* and *Botrytis cinerea*, whereas SA-signaling mutants did not (Thomma *et al.* 1998, Thomma *et al.* 1999). Furthermore, ET-insensitive tobacco and *Arabidopsis* plants have been shown to be more susceptible to a range of necrotizing pathogens, e.g. *B. cinerea*, *Pythium* spp. and *Fusarium* spp. (Geraats *et al.* 2002). Some pathogens are resisted by a SA-dependent mechanism, as well as JA- and ET-dependent mechanisms, e.g. *Pseudomonas syringae* pv. *tomato* DC3000 (*Pst* DC3000) and *Xanthomonas campestris* pv. *armoraciae* (Delaney *et al.* 1994, Pieterse *et al.* 1998, Ton *et al.* 1998, Ellis *et al.* 2002, Ton *et al.* 2002b). Certain pathogens are resisted by the hormones acting sequentially, e.g. *Xanthomonas campestris* pv. *vesicatoria* in tomato (O'Donnell *et al.* 2003). In this interaction, JA, ET and SA are required in succession. These results clearly demonstrate the intertwining of several signal transduction pathways in basal resistance. Moreover, it shows that the roles of different hormones vary depending on the plant-pathogen interaction.

Within plant species, individuals can vary in their level of resistance to a certain pathogen, with some individuals being fully resistant. Such resistance can usually be described by a gene-for-gene relationship. A pathogen carrying a specific avirulence (*AVR*) gene is recognized only by a plant carrying a corresponding resistance (*R*) gene. In such an incompatible interaction, the pathogen usually triggers a rapid and local defense response that leads to a hypersensitive reaction. The hypersensitive reaction is often regarded as a form of programmed cell death that

**Abbreviations:** ABA, abscisic acid; BABA,  $\beta$ -aminobutyric acid; BTH, benzothiadiazole; ET, ethylene; INA, 2,6-dichloroisonicotinic acid; ISR, induced systemic resistance; JA, jasmonic acid; NPR1, non-expresser of PR genes 1; PGPR, plant growth-promoting rhizobacteria; PGPF, plant growth-promoting fungi; PR, pathogenesis-related; *Pst* DC3000, *Pseudomonas syringae* pv. *tomato* strain DC3000; SA, salicylic acid; SAR, systemic acquired resistance

is dependent on e.g. reactive oxygen species. The resulting small necrotic lesion is involved in preventing the pathogen from spreading any further (Dangl *et al.* 1996). Furthermore, deposition of anti-microbial compounds, strengthening of cell walls and expression of defense-related genes in the vicinity of the lesion all contribute to the restriction of the pathogen (Hammond-Kosack and Jones 1996). Non-host resistance, basal resistance and *R*-gene mediated resistance play an important role in the plant's innate immune response. The mechanisms involved in these types of disease resistance have been extensively reviewed (Slusarenko *et al.* 2000). This review focuses on induction, signaling and expression of systemically induced, broad-spectrum disease resistance.

## 2. INDUCED DISEASE RESISTANCE

### 2.1. Biological and chemical induction of disease resistance

During evolution plants have developed sophisticated defensive strategies to perceive pathogen attack and to translate this perception into an appropriate adaptive response. When under attack, a plant is capable of enhancing its resistance, and this condition is often referred to as induced, or acquired, resistance. Acquired disease resistance is thought to involve an enhancement of basal resistance (Van Loon 2000, Ton *et al.* 2002b). A classic example of biologically induced disease resistance is triggered after attack by a necrotizing pathogen (Ross 1961). This attack renders distant, uninfected plant parts more resistant towards a broad spectrum of virulent pathogens (Kuc 1982, Ryals *et al.* 1996, Sticher *et al.* 1997). The onset of this enhanced resistance, known as systemic acquired resistance (SAR), is accompanied by a local and systemic increase in SA levels (Malamy *et al.* 1990, Métraux *et al.* 1990). Subsequently, a large set of SAR genes, including genes encoding pathogenesis-related (PR) proteins, is up-regulated (Ward *et al.* 1991, Van Loon 1997, Van Loon and Van Strien 1999). These PR genes are often considered as marker genes for SAR expression. Several PR-proteins possess anti-microbial activity and are thought to contribute to the state of resistance attained. The PR proteins can accumulate to levels from 0.3 up to 1% of the total protein content of the leaf (Lawton *et al.* 1995).

A large variety of chemicals have been shown to activate the SAR response. Benzothiadiazole (BTH), 2,6-dichloroisonicotinic acid (INA), and SA induce the same set of PR genes comparable to biologically-induced SAR (Ward *et al.* 1991, Uknes *et al.* 1992, Lawton *et al.* 1996). Using parsley cells as a model, SAR induction by the commercially available plant activator BION and the biological agent Milsana, as well as a large group of related chemicals, was demonstrated (Siegrist *et al.* 1998).

A second, well-studied biologically-induced disease resistance occurs after root colonization by selected strains of non-pathogenic *Pseudomonas* spp. (Van Peer *et al.* 1991, Wei *et al.* 1991). This type of resistance is generally called rhizobacteria-induced systemic resistance (ISR, Pieterse *et al.* 1996, Van Loon *et al.* 1998). ISR has been demonstrated in different plant species against several pathogens under conditions where the rhizobacteria and the pathogen remained spatially separated (Van Loon *et al.* 1998, Pieterse *et al.* 2002). The expression of rhizobacteria-mediated ISR was shown to be independent of the presence of SA or enhanced PR-gene expression. Phenotypically, rhizobacteria-mediated ISR resembles pathogen-induced SAR. Although the terms SAR and ISR are synonymous (Hammerschmidt *et al.* 2001), for convenience we distinguish between pathogen- and rhizobacteria-induced resistance by using the term SAR for the pathogen-induced type and ISR for the rhizobacteria-induced type of resistance. The non-protein amino acid  $\beta$ -aminobutyric acid (BABA) appears to have a different mode of action. Like ISR, it induces resistance without the expression of PR-genes (Cohen and Gisi 1994, Zimmerli *et al.* 2001). However, BABA can induce resistance to *H. parasitica* in *Arabidopsis* independent of SA, JA or ET, through a signaling pathway that requires abscisic acid (ABA) and involves priming for callose deposition (Ton and Mauch-Mani 2004, Ton *et al.* 2005). On the other hand, BABA-induced resistance against the bacterial pathogen *Pst* DC3000 and the fungal pathogen *B. cinerea* is SA dependent (Zimmerli *et al.* 2000, Zimmerli *et al.* 2001).

### 2.2. Systemic acquired resistance

After local infection by a necrotizing pathogen leading to an HR, the enhanced state of resistance extends systemically into the uninfected plant parts. During the onset of SAR, a locally altered transcriptional response precedes the hypersensitive reaction and a second wave of transcriptional reprogramming, not apparent in a virulent attack, marks the transition from basal to induced resistance (de Torres *et al.* 2003). The induction of SAR is accompanied by local and systemic accumulation of endogenous levels of the plant hormone SA, followed by PR-gene expression (Malamy *et al.* 1990, Métraux *et al.* 1990). The importance of the accumulation of SA for the expression of SAR was demonstrated by using transgenic NahG plants. These plants express the bacterial salicylate hydroxylase *nahG* gene, making them incapable of accumulating SA (Gaffney *et al.* 1993). NahG plants do not show a SAR response (Ryals *et al.* 1996). Exogenous application of SA, or one of its functional analogs BTH or INA, leads to the full expression of SAR. Likewise, SA production-deficient mutants *sid1* (also called *eds5*) and *sid2* (also known as *eds16*) do not show a SAR response after infection with a necrotizing pathogen (Fig. 1; Rogers and Ausubel 1997, Nawrath and Métraux, Wildermuth *et al.* 2001). These results indicate that SA is necessary and sufficient for the induction of SAR. In tobacco, up to 70% of the SA accumulating in non-infected leaves may originate from the infected leaves (Shulaev *et al.* 1995). The remaining SA is produced *de novo* in stems and petioles in response to a mobile signal (Smith-Becker *et al.* 1998). Even though SA is transported, grafting experiments between tobacco wild-type and NahG plants showed that SA is not the transported signal responsible for the systemic nature of SAR. However, SA is needed in non-infected tissues to effectively express SAR (Vernooij *et al.* 1994, Willits and Ryals 1998). As shown recently, ET perception is required to generate the systemic signal, but is not needed for the response to the systemic signal leading to SAR (Verberne *et al.* 2003). Instead, a putative apoplastic lipid transfer protein (DIR1) was characterized, which is thought to interact with a lipid-derived molecule to promote long distance signaling during SAR (Maldonado *et al.* 2002).

Transduction of the SA signal into PR-gene expression and enhanced resistance requires the regulatory protein NPR1 (Cao *et al.* 1994). Mutant *npr1* plants accumulate normal levels of SA after pathogen attack, but are incapable of transducing this SA accumulation into a response leading to PR-gene expression and SAR. Moreover, treatment of *npr1* with SA or its analogue INA does not lead to induction of resistance. These results indicate that NPR1 is acting downstream of SA in the SAR signal transduction pathway (Fig. 1; Cao *et al.* 1994). Since the discovery of the NPR1 gene, several mutant screens based on impaired SAR expression (Delaney *et al.* 1995), reduced SA-induced PR-gene expression (Shah *et al.* 1997), or enhanced disease susceptibility (Glazebrook *et al.* 1996) identified mutations allelic to the *npr1* mutation. These

results further illustrate the importance of the *NPR1* gene in SAR. The *NPR1* gene encodes a protein with a BTB/POZ (for Broad-complex, Tramtrack and Bric-a-brac/Poxygen and Zinc fingers) (Harrison and Travers 1990, DiBello *et al.* 1991, Koonin *et al.* 1991, Godt *et al.* 1993) and an ankyrin-repeat domain (Cao *et al.* 1997, Ryals *et al.* 1997, Aravind and Koonin 1999). Both domains have previously been shown to be important in protein-protein interactions (Bork 1993). In non-induced plants, NPR1 is present as a multimer through forming intermolecular disulfide bonds (Mou *et al.* 2003). During the induction of SAR, SA triggers a biphasic change in cellular redox potential that leads to reduction of the disulfide bonds. This results in conversion of NPR1 into a monomeric form. These monomers are translocated into the nucleus (Kinkema *et al.* 2000), where they interact with members of the TGA/OBF subclass of basic-leucine-zipper (bZIP) transcription factors. These transcription factors are involved in SA-dependent activation of PR-genes (Lebel *et al.* 1998, Zhang *et al.* 1999, Després *et al.* 2000, Niggeweg *et al.* 2000, Zhou *et al.* 2000, Subramaniam *et al.* 2001, Fan and Dong 2002, Zhang *et al.* 2003). A direct interaction between NPR1 and specific TGA transcription factors is required for binding of the complex to elements within the promoter of the PR-genes (Després *et al.* 2000, Fan and Dong 2002). Overexpression of the *NPR1* gene leads to an enhanced resistance to pathogen attack (Cao *et al.* 1998, Friedrich *et al.* 2001).

## 2.3. Rhizobacteria-induced systemic resistance

### 2.3.1. SA- or stress-dependent enhancement of resistance

Plants produce exudates and lysates at their root surface, where rhizobacteria are attracted in large numbers (Lynch and Whipps 1991, Lugtenberg *et al.* 2001, Walker *et al.* 2003). Selected strains of non-pathogenic rhizobacteria are named plant growth-promoting rhizobacteria (PGPR), because they possess the capability to stimulate plant growth (Kloepper *et al.* 1980, Pieterse and Van Loon 1999, Bloemberg and Lugtenberg 2001, Pieterse *et al.* 2003). *Pseudomonas* spp. are among the most effective PGPR. Moreover, they have been shown to be responsible for the reduced activity of soil-borne pathogens in disease-suppressive soils (Raaijmakers and Weller 1998, Weller *et al.* 2002, Duff *et al.* 2003). This type of biological control can be the result of competition for nutrients, siderophore-mediated competition for iron, antibiosis or the production of lytic enzymes (Bakker *et al.* 1991, Van Loon and Bakker 2003). Apart from such direct antagonistic effects on soil-borne pathogens, some PGPR strains are also capable of reducing disease incidence in above-ground plant parts through plant-mediated mechanisms. Under iron-limiting conditions, certain rhizobacterial strains produce SA as an additional siderophore (Meyer *et al.* 1992, Visca *et al.* 1993). The enhanced defensive capacity elicited by *Pseudomonas fluorescens* CHA0 in tobacco might be fully explained by the bacterial production of SA, which could elicit a SAR response. Treatment of tobacco roots with CHA0 triggers accumulation of SA-inducible PR proteins in the leaves (Maurhofer *et al.* 1994). Moreover, transformation of the SA-biosynthetic gene cluster of CHA0 into *Pseudomonas fluorescens* P3 improved the systemic resistance inducing-capacity of this strain (Maurhofer *et al.* 1998).

Another strain that has been suggested to elicit a SA-dependent enhanced defensive capacity is *Pseudomonas aeruginosa* 7NSK2. A SA-deficient mutant of this bacterium failed to induce resistance in bean and tobacco (De Meyer and Höfte 1997). Moreover, 7NSK2 was unable to induce resistance in NahG tobacco plants against TMV (De Meyer *et al.* 1999). A SA overproducing mutant of 7NSK2 was shown to trigger the SA-dependent SAR pathway by producing SA at the root surface (De Meyer and Höfte 1997). Recently, however, Audenaert *et al.* (2002) showed that the secondary siderophore pyochelin and the antibiotic pyocyanin are the determinants for the enhanced resistance induced by wild-type 7NSK2. SA is an intermediate in the formation of pyochelin and the combination of pyocyanin and pyochelin is toxic to root cells, thereby setting off the SAR response.

General stresses can also induce similar responses. Cartieaux *et al.* (2003) performed a transcriptome analysis of *Arabidopsis* roots and shoots upon colonization of the roots by *Pseudomonas thivervalensis* (strain MLG45). MLG45 induced a clear growth reduction under the conditions used (Persello-Cartieaux *et al.* 2001, Cartieaux *et al.* 2003), suggesting that systemic changes in gene expression observed were due to a more general stress response. A significant increase in defense-related transcripts was detected prior to challenge inoculation, whereas very few changes in the transcriptome of roots were apparent, suggesting that the systemic changes in gene expression observed in MLG45-induced plants are primarily related to stress-induced reduction of plant growth.

### 2.3.2. Bacterial-plant interactions involved in ISR

Other strains of fluorescent *Pseudomonas* spp. have been shown to trigger ISR in an SA-independent manner (Pieterse and Van Loon 1999). SA-independent ISR has been shown in *Arabidopsis* (Van Wees *et al.* 1997, Iavicoli *et al.* 2003, Ryu *et al.* 2003), cucumber (Wei *et al.* 1991), tobacco (Press *et al.* 1997, Zhang *et al.* 2002), radish (Leeman *et al.* 1995a), and tomato (Yan *et al.* 2002). This wide range of induction of ISR indicates that the ability of these *Pseudomonas* strains to activate a SA-independent pathway controlling systemic resistance is common to a broad range of plants. ISR-inducing rhizobacteria show little specificity in their colonization of roots of different plant species (Van Loon *et al.* 1998). In contrast, the ability to induce ISR appears to be dependent on the bacterium/host combination. For instance, *Pseudomonas*

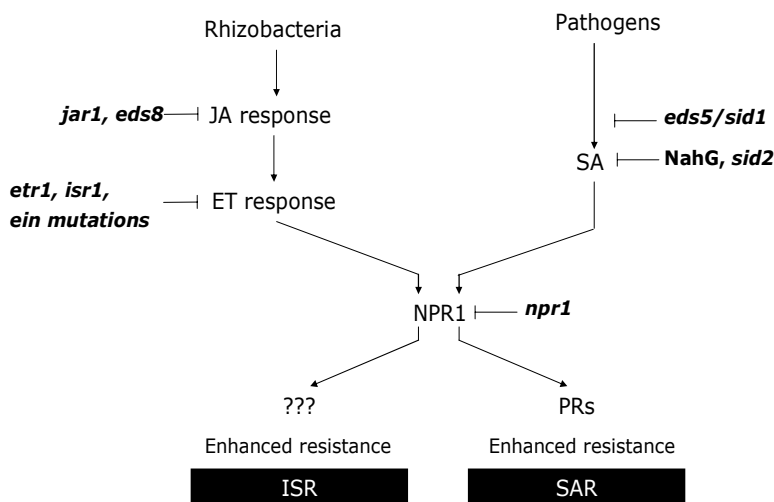


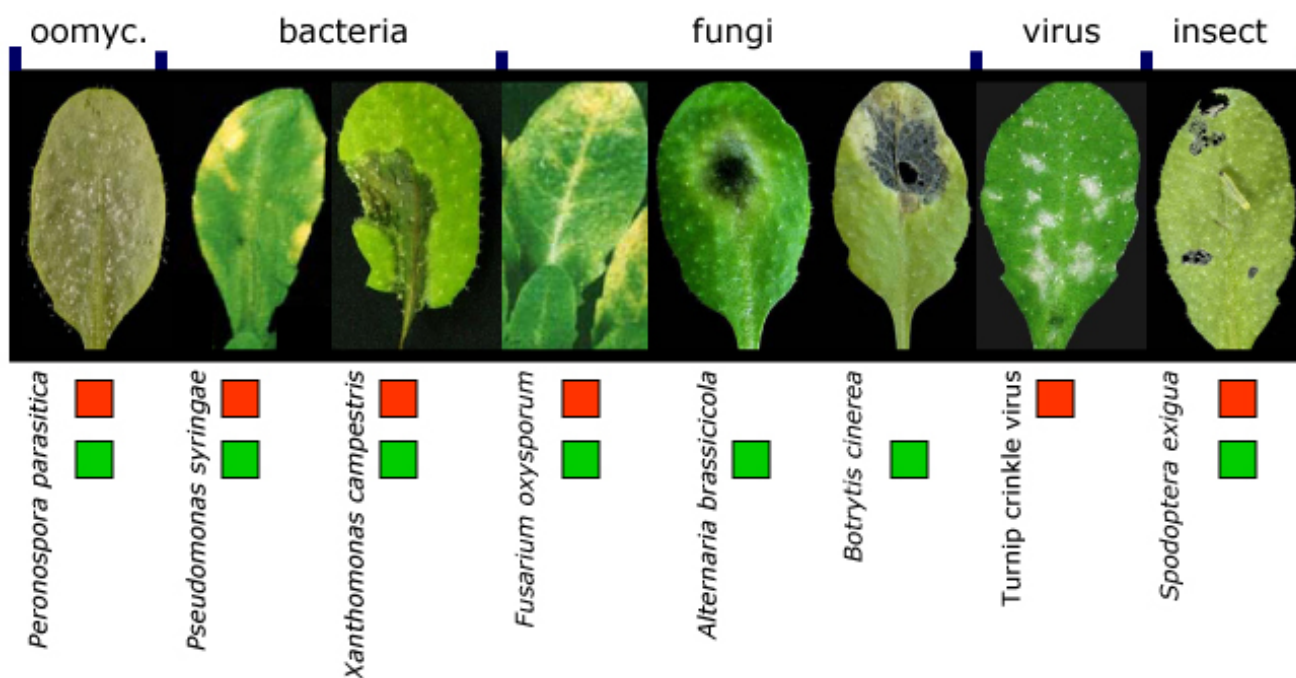
Fig. 1 Schematic representation of the signal transduction pathways leading to rhizobacteria-mediated ISR and pathogen-induced SAR.

*fluorescens* WCS374r is capable of inducing ISR in radish, but not in *Arabidopsis* (Leeman *et al.* 1995a, Van Wees *et al.* 1997). Conversely, *Arabidopsis* is responsive to *Pseudomonas putida* WCS358r, while radish is not (Van Peer *et al.* 1991, Van Peer and Schippers 1992, Leeman *et al.* 1995a, Van Wees *et al.* 1997). *Pseudomonas fluorescens* WCS417r is capable of inducing ISR in both *Arabidopsis* and radish (Van Wees *et al.* 1997), as well as in other species, i.e. carnation (Van Peer *et al.* 1991), radish (Leeman *et al.* 1995a), tomato (Duijff *et al.* 1998), and bean (Bigirimana and Höfte 2002).

Besides differences in inducibility between species, there can also be differences within species. *Arabidopsis* accessions Columbia (Col-0) and Landsberg *erecta* (Ler-0) are responsive to ISR induction by WCS417r, while accessions Wassilewskija (Ws-0) and RLD1 are not (Van Wees *et al.* 1997, Ton *et al.* 1999, Ton *et al.* 2001, Pieterse *et al.* 2002). Apparently, these accessions are compromised in a step between the recognition of the bacterium and expression of ISR. Moreover, these data indicate that ISR is genetically determined. Up until now, several compounds have been implicated in the elicitation of ISR (Van Loon *et al.* 1998, Bakker *et al.* 2003). Apart from live WCS417r bacteria, also dead bacteria are capable of inducing ISR, indicating that bacteria do not need to be metabolically active to induce ISR. Cell wall preparations, purified lipopolysaccharide, siderophores, antibiotics, and flagella all are capable of inducing systemic resistance (Van Peer and Schippers 1992, Leeman *et al.* 1995b, Van Wees *et al.* 1997, Bakker *et al.* 2003, Iavicoli *et al.* 2003). Because of these multiple inducing determinants, bacterial mutants lacking flagella or the O-antigenic side chain of the lipopolysaccharide were still able to elicit ISR in *Arabidopsis* (Van Wees *et al.* 1997, Bakker *et al.* 2003). So far, putative receptors for the bacterial cell wall preparations have not been isolated. However, a sensitive perception mechanism for bacterial flagellins has been identified (Felix *et al.* 1999). A receptor kinase was characterized that shares homology with known plant disease resistance genes (Gomez-Gomez and Boller 2000), suggesting that bacteria are recognized similar to plant pathogens.

### 2.3.3. Range of ISR effectiveness

The plant-growth promoting WCS417r (Pieterse and Van Loon 1999) has been shown to induce resistance in *Arabidopsis* against a broad range of pathogens (Van Loon *et al.* 1998, Pieterse *et al.* 2002, Pieterse *et al.* 2003). This makes ISR phenotypically comparable to pathogen-induced SAR (Kuc 1982). Like classic pathogen-induced SAR, colonization of roots by WCS417r leads to ISR against different types of pathogens, including the fungal root pathogen *F. oxysporum* f.sp. *raphani*, the oomycetous leaf pathogen *H. parasitica*, and the bacterial leaf pathogens *Xanthomonas campestris* pv. *armoraciae* and *Pst* DC3000 (Fig. 2; Pieterse *et al.* 1996, Van Wees *et al.* 1997, Ton *et al.* 2002b). In contrast to SAR, treatment of *Arabidopsis* with WCS417r does not lead to systemic resistance against turnip crinkle virus. Conversely, ISR appears to be highly effective against the fungal pathogen *A. brassicicola*, whereas SAR is not (Ton *et al.* 2002b). The spectra of effectiveness of ISR and SAR partly overlap, but are also clearly divergent. This indicates a different mechanism of rhizobacteria-mediated ISR compared to the classic SAR response. This different mode of action was further apparent from the simultaneous activation of the ISR and SAR pathways. This results in an enhanced level of protection against *Pst* DC3000, compared to each treatment alone (Van Wees *et al.* 2000).



**Fig. 2** Effectiveness of rhizobacteria-mediated ISR (green squares) and pathogen-induced SAR (red squares) in *Arabidopsis*. Photographs depict symptoms in uninduced wild-type *Arabidopsis* plants upon infection or infestation of the pathogens and insects indicated. Squares underneath the photographs indicate that ISR and/or SAR confer a significant level of resistance. Results are based on studies by Pieterse *et al.* (1996 1998 2002), Van Wees *et al.* (1997 2000), Ton *et al.* (2002a 2002b) and (CMJ Pieterse, JA Van Pelt, VR Van Oosten, and S Van der Ent, unpublished results).

### 2.3.4. Rhizobacteria-mediated ISR: signal transduction

The differential range of effectiveness of ISR, compared to SAR, indicates the involvement of different mechanisms. Pathogen-induced SAR is accompanied by both local and systemic increases in SA levels and the expression of *PR*-genes (Van Loon and Van Strien 1999, Métraux 2001). Compelling evidence that rhizobacteria-mediated ISR is a SA-independent defense response came from experiments with SAR-compromised NahG plants. Upon colonization of the roots by ISR-inducing WCS417r bacteria, *Arabidopsis* NahG plants expressed normal

levels of ISR (Pieterse *et al.* 1996, Van Wees *et al.* 1997). Furthermore, WCS417r-induced radish plants did not accumulate PR-proteins in association with their enhanced defensive capacity against fusarium wilt disease (Hoffland *et al.* 1995). Moreover, WCS417r-induced, ISR expressing *Arabidopsis* plants showed enhanced resistance against *Pst* DC3000 and *F. oxysporum* f.sp. *raphani*, without activation of the SAR marker genes *PR-1*, *PR-2*, and *PR-5* (Pieterse *et al.* 1996, Van Wees *et al.* 1997), and analysis of SA levels revealed no changes after ISR induction, neither locally nor systemically (Pieterse *et al.* 2000). Taken together, it was concluded that WCS417r-mediated ISR in *Arabidopsis* is regulated by a SA-independent signaling pathway.

Further studies revealed that treatment of the roots with WCS417r failed to trigger ISR in JA-insensitive *jar1* plants or ET-insensitive *etr1* plants. This indicated that the JA- and ET-response pathways are essential for the establishment of ISR (Fig. 1; Pieterse *et al.* 1998, Pieterse *et al.* 2000). Another indication for the involvement of the JA-signaling pathway came from the analysis of *Arabidopsis* mutant *eds8*, which was previously shown to exhibit enhanced susceptibility to *P. syringae* (Glazebrook *et al.* 1996). This mutant is impaired both in WCS417r-mediated ISR (Ton *et al.* 2002c), and JA-signaling (Ton *et al.* 2002b, Glazebrook *et al.* 2003). To further elucidate the role of ET in the ISR signaling pathway, a large set of well-characterized ET-signaling mutants was analyzed. None of these mutants showed an ISR response against *Pst* DC3000 after colonization of the roots by WCS417r (Knoester *et al.* 1999). These results confirmed that an intact ET-signaling pathway is required for the establishment of ISR. Particularly interesting was the analysis of the *eir1* mutant, which is ET-insensitive in the roots, but not in the shoot. This *eir1* mutant is incapable of showing ISR after root colonization by WCS417r. In contrast, after leaf infiltration with WCS417r, it did show ISR indicating that responsiveness to ET is required at the site of induction (Knoester *et al.* 1999). However, these results do not exclude the possibility that the ET response is also needed during the expression of ISR upon challenge inoculation.

Further evidence for the involvement of the ET-response pathway came from the identification of the *Arabidopsis* *ISR1* locus (Ton *et al.* 1999). Genetic analysis of the progeny of a cross between the WCS417r-responsive ecotype Col-0 and the ISR-impaired ecotype RLD1 revealed that both the potential to express ISR and basal resistance against *Pst* DC3000 are monogenic, dominant traits that are genetically linked. The *ISR1* locus is required for effective ISR against several different pathogens (Fig. 1; Ton *et al.* 2002a). Interestingly, analysis of the ISR-impaired ecotype RLD1 revealed that it has a reduced sensitivity to ET, which co-segregates with the *ISR1* locus (Ton *et al.* 2001). These results strongly indicate that the *Arabidopsis* *ISR1* locus encodes a novel component in the ET-signal transduction pathway that is important in both basal resistance and ISR in *Arabidopsis*.

Both at the site of application of the bacteria and systemically in the leaves, the JA content and the ET evolution remained unaltered upon ISR induction (Knoester *et al.* 1999, Pieterse *et al.* 2000). Moreover, *LOX2* co-suppressed S-12 plants, which are blocked in the increase of JA after wounding (Bell *et al.* 1995) and pathogen infection (Pieterse *et al.* 2000), were normally responsive to WCS417r. Nevertheless, resistance comparable to ISR can be induced chemically by application methyl jasmonate (MeJA) or the ET precursor 1-aminocyclopropane-1-carboxylate (ACC). MeJA induction of resistance was blocked in the *jar1* and *etr1* mutants. In contrast, the ACC-induced expression of resistance was blocked in *etr1*, but not in *jar1*. Therefore, it was postulated that WCS417r-mediated ISR is regulated by a signaling pathway with the requirement for JA-signaling preceding the ET-signaling response (Fig. 1; Pieterse *et al.* 1998).

To determine whether ISR is associated with increased JA- or ET-responsive gene expression, the expression of a large set of well-known JA- and ET-responsive genes (e.g. *VSP2*, *PDF1.2*, *LOX1*, *LOX2*, *HEL*, *CHI-B*, and *PAL*) was analyzed in WCS417r-induced *Arabidopsis* plants. None of these genes tested showed an up-regulation, neither locally in the roots, nor systemically in the leaves (Van Wees *et al.* 1999). These results indicate that the enhanced defensive state during WCS417r-mediated ISR is not associated with enhanced JA- or ET-dependent gene expression. Because ISR is not associated with enhanced levels of the hormone signals JA or ET (Pieterse *et al.* 2000), but nevertheless requires responsiveness to JA and ET (Pieterse *et al.* 1998), it was suggested that ISR is based on an enhanced sensitivity to these hormones, rather than on an increase in their production (Fig. 1).

## 2.4. Dual role for NPR1 in SAR and ISR

To investigate the possible involvement of the SAR regulatory protein NPR1 in ISR signaling, the *Arabidopsis* *npr1* mutant was tested in the ISR bioassay. Surprisingly, the *npr1* mutant was incapable of showing WCS417r-mediated ISR (Pieterse *et al.* 1998). This result clearly showed that WCS417r-mediated ISR, like SA-dependent SAR, is an NPR1-dependent defense response (Fig. 1). Further analysis of the ISR signal-transduction pathway revealed that NPR1 acts downstream of the JA- and ET-response pathways (Pieterse *et al.* 1998). Because SAR is associated with NPR1-dependent *PR*-gene expression, and ISR is not, this demonstrates that NPR1 must differentially regulate gene expression, depending on the signaling pathway that is activated upstream of it. NPR1 seems not a limiting factor since simultaneous activation of ISR and SAR leads to an enhanced defensive activity compared to that observed with either type of induced resistance alone (Van Wees *et al.* 2000). These results suggest that the NPR1 protein is important in regulating and intertwining different hormone-dependent defense pathways.

Apart from its role in SA-dependent gene expression, NPR1 was also shown to be involved in the negative regulation of the JA-response by SA (Spoel *et al.* 2003). Whereas nuclear localization of NPR1 is needed for SA-induced *PR-1* gene expression (Kinkema *et al.* 2000), the SA-induced, NPR1-mediated negative effect on JA-responsive gene expression is exerted through an as yet uncharacterized function in the cytosol (Spoel *et al.* 2003). These results indicate that NPR1 can have different functions at different locations in the cells.

## 3. GENE EXPRESSION ANALYSIS

### 3.1. Transcriptome analysis of SAR

All the different large-scale analyses of the transcriptome of *Arabidopsis* show that plants react with major changes to different pathogens, like *Psm* ES4326 and *A. brassicicola*, and stimuli, like JA, the ET precursor ACC, and SA (Schenk *et al.* 2000, Cheong *et al.* 2002, Glazebrook *et al.* 2003, Katagiri and Glazebrook 2003, Schenk *et al.* 2003, Tao *et al.* 2003, Van Wees *et al.* 2003, De Vos *et al.* 2005). Northern blot analysis confirmed a limited set of SAR marker genes (Ward *et al.* 1991, Ryals *et al.* 1996). Using a small set of *Arabidopsis* enhanced sequenced tags (EST's), Schena *et al.* (1995) made the DNA microarray technology accessible for plant research, making it possible to examine the expression of a large group of genes simultaneously. Since then, and aided by the full sequencing of the *Arabidopsis* genome (Kaul *et al.* 2000), many

microarray service centers have been established, which now provide a range of different small microarrays up to complete genome arrays (Reymond 2001, Zhu 2003). Using a DNA microarray representing about 25% of all *Arabidopsis* genes, Maleck *et al.* (2000) monitored gene expression after treatment of wild type and different SAR-impaired mutants with several different SAR inducers. About 300 (4.3%) out of the 7,000 genes were shown to be involved in the SAR response. These results indicate that expression of SAR leads to a much larger transcriptional reprogramming than just the changes in *PR*-gene expression observed by conventional methods. Moreover, Maleck and co-workers (2000) provided evidence for a common promoter element in a set of coordinately regulated genes, including *PR-1*. In addition, they showed that subtle differences in gene expression patterns occur under different SAR-inducing and repressing conditions, indicating that although every treatment leads to SAR, induction is accompanied by additional treatment-specific gene expression. Moreover, gene expression during the SAR response was found to partly overlap with responses observed during a compatible interaction. This paradox is thought to be explained by the fact that during a compatible interaction, host defense responses are turned on, but too slowly or too late to be effective. These results support the idea that acquired resistance is an enhancement of basal resistance, and involves the same resistance mechanisms (Van Loon 2000).

### 3.2. Transcriptome analysis of ISR

To identify ISR-related genes, Léon-Kloosterziel *et al.* (2005) screened a large number of gene trap and enhancer trap lines of *Arabidopsis* for WCS417r-induced gene expression. This resulted in the isolation of an enhancer trap line with WCS417r-induced *GUS* expression in the roots. Further study revealed that this induction occurs upon colonization of the roots by different non-pathogenic *Pseudomonas* spp. strains, but not after colonization by *Escherichia coli*. Moreover, *GUS* expression was also observed after treatment with ACC, but not with JA or SA. Analysis of the flanking sequences revealed that the *GUS* gene was activated in *cis* by the thaumatin-like gene *AtTLP1*, which encodes a pathogenesis-related protein of the PR-5 family. However, analysis of an *AtTLP1* knockout mutant indicated that WCS417r-induced expression of this gene is not required for the expression of ISR against *Pst* DC3000. Moreover, overexpression of the *AtTLP1* gene did not result in a constitutive or enhanced ISR response. These results indicate that *AtTLP1* gene expression is a common response of *Arabidopsis* roots to non-pathogenic *Pseudomonas* bacteria, but it is unlikely that the AtTLP1 protein contributes to the enhanced defensive capacity observed in ISR-expressing plants.

Verhagen *et al.* (2004) analyzed the transcriptome of *Arabidopsis* during WCS417r-mediated ISR induction and expression using Affymetrix GeneChips containing about one third of the genes present in the *Arabidopsis* genome. Colonization of the roots by WCS417r resulted in changes in expression of a large group of genes locally in the roots. Part of these changes was transient and only visible at a single time point, whereas 97 genes showed consistent changes in time. This group is thought to be involved in the local onset of ISR. Systemically in ISR expressing leaves, prior to pathogen challenge, none of the ~8,000 genes tested showed consistent changes in expression. These observations indicate that the state of ISR, in contrast to SAR, is not associated with detectable changes in gene expression. Gene expression patterns were also determined after challenge inoculation with *Pst* DC3000. In non-induced, infected control plants, a large set of genes showed changes in expression after pathogen challenge. Part of this set is thought to be important for basal resistance against *Pst* DC3000. Also in ISR-expressing plants, a large group of genes showed altered expression levels. This group was slightly smaller in number, perhaps because of the enhanced resistance in ISR-expressing plants. In challenged control plants, these general *Pst* DC3000-responsive genes were shown to be predominantly dependent on JA/ET and SA signal transduction. A group of 81 of these – mainly JA/ET-dependent – genes showed augmented expression in ISR-expressing plants, indicating that these genes were primed to respond faster and/or more strongly upon pathogen attack. The majority of the primed genes was predicted to be regulated by JA and/or ET signaling, which confirmed earlier findings that colonization of the roots by WCS417r primed *Arabidopsis* plants for augmented expression of the JA- and/or ET-responsive genes *AtVSP2*, *PDF1.2* and *HEL* (Van Wees *et al.* 1999, Hase *et al.* 2003). Other ISR-inducing PGPR have also been demonstrated to enhance the plant's defensive capacity by priming for potentiated defense-related gene expression (e.g. De Meyer *et al.* 1999, Ahn *et al.* 2002, Kim *et al.* 2004, Tjamos *et al.* 2005), indicating that this is a common feature in rhizobacteria-mediated ISR. These results demonstrate that WCS417r-mediated ISR is associated with potentiation of gene expression. Priming of pathogen-induced genes allows the plant to react more effectively to the invader encountered, which might explain the broad-spectrum action of rhizobacteria-mediated ISR.

### 3.3. Priming in other beneficial plant-microbe interactions

Besides pathogenic interactions, mutually beneficial relationships are frequent in nature, improving plant nutrition and/or helping the plant to overcome biotic or abiotic stresses. These associations can involve fungi, such as mycorrhizal and plant growth-promoting fungi (PGPF), or bacteria, such as the nitrogen-fixating *Rhizobium* spp., or plant growth-promoting rhizobacteria (PGPR) (Van Loon *et al.* 1998, Kloepper *et al.* 2004, Bent 2005, Harrison 2005). The establishment of mutualistic associations involves mutual recognition and a high degree of coordination that is based on a continuous cellular and molecular dialogue between the plant and the micro-organism. In many cases, recognition of a beneficial micro-organism by the plant induces an enhanced defensive capacity in the plant that effectively protects the plant against a broad spectrum of plant pathogens (Pozo *et al.* 2005, and references herein). For instance, colonization of tomato roots by the mycorrhizal fungus *Glomus mosseae* systemically protects the plant against infection by *Phytophthora parasitica* (Cordier *et al.* 1998, Pozo *et al.* 2002). In general, systemic resistance induced by beneficial micro-organisms is not associated with major changes in defense-related gene expression (Pieterse *et al.* 2002), probably because this would entail heavy investments in host resources and reduced fitness (Heil 2002), which would undermine the mutual benefits of the interaction.

A common feature of resistance induced by beneficial micro-organisms is priming. For instance, colonization of tomato roots by mycorrhizal fungi systemically protects the plant against *H. parasitica* infection, but it does not directly induce systemic accumulation of PR proteins. However, upon pathogen attack, mycorrhizal plants accumulate significantly more PR-1a and basic  $\beta$ -1,3 glucanase protein than non-mycorrhizal plants. Ultrastructural studies revealed that mycorrhizal plants deposited host cell wall thickenings containing non-sterified pectins and callose around the sites of pathogen infection, whereas non-mycorrhizal plants did not (Cordier *et al.* 1998, Pozo *et al.* 1999, Pozo *et al.* 2002). Similarly, PGPF, such as *Trichoderma* spp., have been shown to induce a primed state in plants. In cucumber, subsequent challenge inoculation of *Trichoderma asperellum* T203-preinoculated plants with the leaf pathogen *Pseudomonas syringae* pv. *lachrymans* resulted in potentiated PR gene expression

relative to non-induced, challenged plants (Shoresh *et al.* 2005). In barley, pre-inoculation of the roots with the PGPF *Piriformospora indica* resulted in enhanced disease resistance and increased tolerance to salt stress without clear changes in defense-related gene expression (Waller *et al.* 2005). Evidence was provided indicating that the primed state was conferred through an enhanced antioxidative capacity that boosts plant defense responses to biotic and abiotic stress.

### 3.4. Priming in plant-pathogen interactions

Priming has emerged as a common feature of different types of induced resistance (Conrath *et al.* 2002). For instance, SAR-non-inducing doses of the synthetic SAR inducer benzothiadiazole (BTH) were shown to enhance two cellular defense responses after *Pst* infection, namely *PAL* gene expression and callose deposition, without inducing these responses by itself. Moreover, priming for potentiated defense gene expression was also found during *Pst* DC3000(*avrRpt2*)-induced SAR against virulent *Pst* DC3000 (Kohler *et al.* 2002). Priming was also shown to be important in the enhancement of resistance by the non-protein amino acid  $\beta$ -aminobutyric acid (BABA). BABA potentiated the accumulation of *PR-1* mRNA after attack by *Pst* DC3000 (Zimmerli *et al.* 2000), but BABA treatment of mutants impaired in the SAR pathway did not result in this potentiation (Zimmerli *et al.* 2000 2001). Recently, BABA-induced priming of defense responses was shown to be regulated through yet another signaling pathway, that depends on abscisic acid (Ton and Mauch-Mani 2004).

Priming can explain, on the one hand, the lack of changes in leaves of ISR-expressing plants prior to pathogen challenge and, on the other hand, why the plant is able to react more effectively when subsequently attacked. Plants in a primed state do not have the metabolic costs of a constantly activated defense response, in contrast to plants in the state of SAR (Heil 2002, Heil and Baldwin 2002). The costs of constant activation of the SAR pathway are apparent in mutant *cpr1* (for *constitutive PR* gene expressor), which constitutively expresses SAR and is much smaller compared to wild-type *Arabidopsis* plants (Bowling *et al.* 1994).

### 3.5. Combining ISR and SAR to improve biocontrol of plant diseases

Plant diseases are responsible for large crop losses in agriculture. Conventional disease control is based on application of chemical agents and resistance breeding. The use of chemical agents and their persistence in soil are potentially harmful to the environment, especially when chemicals are applied repeatedly in large amounts such as in the control of soil-borne fungal pathogens. Classic resistance breeding depends on the availability of resistance genes, which often show limited durability. Moreover, both these disease control strategies are directed against a single or a small group of plant pathogens. Induced disease resistance is an attractive alternative form of plant protection, as it is based on the activation of extant resistance mechanisms in the plant and is effective against a broad spectrum of plant pathogens (Kuc 1982, Van Loon *et al.* 1998). Therefore, detailed knowledge of the molecular mechanisms underlying induced disease resistance will be instrumental in developing biologically-based, environmentally-friendly, and durable crop protection.

Previously, we demonstrated that simultaneous activation of ISR and SAR results in an enhanced level of induced protection against *Pst* DC3000 (Van Wees *et al.* 2000). This indicates that the JA/ET-dependent ISR pathway and the SA-dependent SAR pathway act independently and additive at the level of protection against this particular pathogen. Moreover, we provided evidence that ISR and SAR confer differential protection against different types of pathogens (Ton *et al.* 2002b). Thus, combining both types of induced resistance can protect the plant against a complementary spectrum of pathogens, and can even result in an additive level of induced protection against pathogens that are resisted through both the JA/ET- and the SA- dependent pathways.

Biological control of plant diseases is still in its infancy, because the level of protection and its consistency are generally not sufficient to compete with conventional methods of disease control. One approach to improve the efficacy and consistency of biological control against soil-borne pathogens is to apply combinations of antagonistic micro-organisms with different mechanisms of action (De Boer *et al.* 1999, Bakker *et al.* 2003). In addition, our findings that the combination of ISR and SAR confers protection against a complementary spectrum of pathogens and results in enhanced levels of protection against specific bacterial pathogens (Van Wees *et al.* 2000), offers great potential for integrating both forms of induced resistance in future agricultural practices.

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