INVITED REVIEW

SYSTEMIC ACQUIRED RESISTANCE AGAINST PLANT VIRUS INFECTIONS: A REALITY?

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Tradition is too confortable an armor to be cast off at the first assault.
Phoebus Aaron Levene, 1931.

SUMMARY

Systemic acquired resistance (SAR) to virus infections should be carefully distinguished from such resistance regarding other plant pathogens. In particular: (*i*) SAR operates against localized virus infection by limiting cell-to-cell spread of virus, through a mechanism involving an accelerated hypersensitive reaction without preventing virus replication; (*ii*) SAR does not operate against systemic virus infection; it neither limits virus replication nor alleviates symptoms. SAR may therefore play an important part in limiting many infectious plant diseases, but must be viewed with less enthusiasm in regard to viruses.

RIASSUNTO

LA RESISTENZA SISTEMICA ACQUISITA CONTRO LE INFEZIONI DA VIRUS DELLE PIANTE: È REALTÀ? Il fenomeno della resistenza sistemica acquisita contro le infezioni da virus delle piante (RSA) viene analizzata criticamente nel più ampio contesto della resistenza contro le altre classi di patogeni infettivi. L'esame dei dati oggettivamente disponibili permette di rilevare due punti fondamentali: (*i*) nell'infezione localizzata, la RSA opera limitando la traslocazione dell'infettività virale da cellula a cellula, secondo un meccanismo analogo, ma verosimilmente accelerato, a quello operante nella reazione di ipersensibilità; (*ii*) la RSA non è operante contro l'infezione sistemica, non inibendo in alcun modo la replicazione né mitigando la patogenesi virale. Questa caratteristica negativa argomenta contro le ottimistiche affermazioni che attribuiscono alla RSA un ruolo funzionale di controllo contro l'intera gamma delle infezioni patogenetiche.

Key words: hypersensitive reaction, plant virus, resistance mechanism.

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INTRODUCTION

Resistance, here understood as any inhibition of virus replication and/or spread, is undoubtedly the most important defence strategy against virus infections in plants and is studied in any programme of disease control. Resistance can sometimes be achieved by one or more strategies: (*i*) introduction of Mendelian genes (conventional genetic resistance; Kegler and Spaar, 1993); (*ii*) introduction of foreign genes derived from viral genomes (pathogen-derived resistance; Baulcombe, 1996); (*iii*) infection with viruses causing mild systemic symptoms (cross protection; Fulton, 1986); (*iv*) infection with viruses giving a hypersensitive reaction (HR), (systemic acquired resistance, SAR; Loebenstein, 1972); (*v*) administration of chemical drugs (chemically-induced resistance; Kessmann *et al.*, 1994). The last two procedures can give forms of resistance that are not heritable but that show certain advantages such as virus aspecificity, no undesirable collateral effects on plant genotype, and no change under selection pressure.

Acquired resistance, first described by Gilpatrick and Weintraub (1952), received a decisive impulse thanks to the work of Frank Ross (1960; 1961; 1966). After a period of investigation characterized by broken promises, SAR again attracted the attention of plant virologists and biochemists in attempts to explain it in terms of signal-exchange between plant and pathogen. In the last decade, a great number of papers have appeared on this subject, together with an overabundance of reviews relating SAR to salicylic acid (SA), to other putative chemical signals, to pathogenesis-related proteins (PRs), etc. (see, for example, Klessig and Malamy, 1994; Kuc, 1995; Ryals *et al.*, 1996; Sticher *et al.*, 1997; van Loon, 1997).

This review specifically concerns SAR to virus infections. The subject has been thoroughly reviewed in the past (Ross, 1966; Loebenstein, 1972; van Loon, 1983; Fraser, 1985; White and Antoniw, 1991), so only work published during the last decade will be considered.

SAR: THE PHENOMENON

Research on SAR to plant pathogens has been carried out on more than 20 plant species, and best characterized in tobacco and cucumber (Kuc and Strobel, 1992). The recent introduction of the *Arabidopsis*-pathogen system (Uknes *et al*., 1992) has given greater impulse to investigations on SAR mechanisms, as this system allows better genetic approaches (Delaney, 1997; Glazebrook *et al*., 1997; Meinke and Koornneef, 1997). *Arabidopsis* seems to behave like tobacco (Gaffney *et al*., 1993) and cucumber (Madamanchi and Kuc, 1991), so the three systems will be considered as a single model.

Activation of SAR begin when infection with pathogens (very often viruses) produces HR through synthesis of a signal transmitted from the infected to uninfected tissues. SAR may be associated with stimulation of particular genes, by means of a second messenger. Neither signal nor messenger are known, but SA seems to be closely involved in the following ways: (*i*) resistant tissues accumulate SA (Malamy *et al*., 1990; Mètraux *et al.,* 1990; Enyedi *et al*., 1992; Uknes *et al*., 1992); (*ii*) tissues treated with SA acquire resistance (Ward *et al*., 1991; Uknes *et al*., 1993); (*iii*) transgenic plants expressing salicylate hydroxylase (which prevents SA synthesis) do not acquire resistance (Gaffney *et al*., 1993) and do not accumulate SAR mRNAs (Lawton *et al*., 1994, 1995); (*iv*) SA and its biologically active analogues induce accumulation of lipid peroxidation products probably *via* SA-free radicals (Anderson *et al*., 1998); (*v*) *Pseudomonas aeruginosa* genes promoting synthesis of SA, when introduced into a strain of *P. fluorescens* which does not produce it, render the strain capable of producing SA and significantly improve its ability to induce SAR in tobacco against tobacco necrosis necrovirus (TNV) (Maurhofer *et al*., 1998).

Other results do not support the idea that SA is the systemic signal for activation of SAR in uninfected tissues: (*i*) inducing leaves could be removed before significant accumulation of SA without preventing SAR and the expression of SAR genes (Rasmussen *et al*., 1991); (*ii*) SA does not seem to be translocated from infected to uninfected resistant tissues (Vernooij *et al*., 1994) [this finding has been challenged by Shulaev *et al.* (1995) and Mölders *et al*. (1996)]; (*iii*) Willits and Ryals (1998) have recently found in uninoculated leaves of tobacco mosaic tobamovirus (TMV) inoculated plants a nearly linear relationship between SA concentration and SAR level. This shows that very low SA concentrations fail to induce SAR, in contrast with previous results obtained by the same group (Vernooy *et al*., 1994) which indicated that SAR was induced by negligible SA concentrations.

Some evidence seems to exclude any role of SA: (*i*) Rüffer *et al*. (1995) did not find any specific binding of SA to catalase and so contested any role of SA as signal or second messenger; (*ii*) Pieterse *et al*. (1996) described a form of SAR independent of SA accumulation and PR-gene expression; (*iii*) Krzymowska *et al*. (1997) showed that transgenic tobacco expressing high catalase activity and low level of hydrogen peroxide retains the same levels of SAR; (*iv*) Smirnov *et al.* (1997) pointed out that transgenic tobacco rootstocks expressing pokeweed antiviral protein acquired resistance against TMV in the absence of SA accumulation.

The situation is therefore rather debatable and the possibility of different mechanisms cannot be excluded. Some plant-encoded proteins such as glucanendohydrolases, thaumatin-like protein and PR-1 have antifungal activity (Linthors, 1991; van Loon, 1997). Considerable research has been directed towards identifying genes involved in plant-pathogen interactions and, in this context, *Arabidopsis* mutants have proved very useful (Ryals *et al*., 1995; Delaney, 1997). Research has mostly concerned SAR against fungal, bacterial and localized virus infections, whereas systemic virus infection has been rather neglected.

SAR AGAINST VIRUS INFECTIONS

To induce SAR, HR represents a considerable experimental facility though it is an unpractical method to 'immunize' plants on a large scale. In addition to HR, SAR can be induced by other means, biological (Ryals *et al*., 1996) or chemical (Ahl, 1991; Kessmann *et al*., 1994). Since HR is the most popular way to induce SAR against virus infection, this section will consider SAR as a component of HR.

SAR AGAINST LOCALIZED VIRUS INFECTION. Since the classic experiments of Ross, SAR has been quantified by counting number and measuring size the of necrotic local lesions produced on resistant and control tissues by challenging viruses. The availability of more modern analytical methods (Jones and Torrance, 1986) permits evaluation of SAR in terms of virus accumulated in lesion tissues, an approximate index of virus replication (Konate *et al*., 1982; Roggero and Pennazio, 1984).

To be effective, SAR must limit virus replication and/or spread. Counting number of lesions is not a reliable method, since numbers can be influenced by other factors (Fraser, 1987), whereas lesion size is useful only to estimate cell-to-cell spread of localized infection.

There is convincing evidence that SAR operates

against cell-to-cell spread of virus but there is only little, and conflicting evidence concerning the effectiveness of SAR to prevent virus replication: (*i)* Stein *et al.* (1985) claimed that, in addition to reduction of lesion size, SAR also inhibited virus replication, but Pennazio and Roggero (1988) questioned the experimental procedure adopted to evaluate virus accumulation into the tissues: (*ii)* Spiegel *et al.* (1989) isolated a protein from the intercellular fluid of induced-resistant tobacco tissue which inhibited TMV replication when applied to protoplasts or leaf discs. The presence of such an inhibitor (isolated and characterized by the group of Gad Loebestein; see Gera *et al*., 1994) in induced resistant tissues was proposed by Spiegel *et al.* (1989) to explain SAR in molecular terms. Pennazio and Roggero (1991a), however, evaluated TMV antigen content, following the protocol of Spiegel *et al*. (1989), and failed to find any effect of SAR on virus accumulation per unit of lesioned tissue; (*iii)* more recently, Uknes *et al.* (1993) stressed that resistant *Arabidopsis* tissues accumulated much less turnip crinkle carmovirus-RNA than controls. However, the results shown in Uknes *et al.* (1993) are not apparently expressed per unit of lesioned tissues. This is fundamental, because only by expressing viral RNA or viral antigen accumulation per unit of lesion tissue can one reliably compare resistant and control tissues; (*iv)* Kees van Loon (1997), who has remarkably contributed to investigating SAR, has recently written (1997) that the size reduction of lesion produced by TMV on hypersensitive tobacco was closely associated with a reduction in virus titre, and quotes as reference Ross (1966). However it seem to us that Ross's conclusion was just the opposite. Ross wrote: '*There was a good correlation between increase in lesion area and increase of infectivity per unit area of leaf. These data indicate the chief limitation to virus increase in both types of leaves in the area that becomes infected (*i.e.*, lesion size). The data do not provide any evidence of the operation of an active virus-inactivating mechanism in resistant leaves. Nor has evidence of marked virus inactivation in resistant leaves been obtained in some preliminary studies on specific infectivity of TMV isolated by differential centrifugation from normal-sized lesions in control leaves and tiny lesions from resistant leaves*'. (Ross, 1966; pp. 141-142).

In contrast with the above results, there is experimental evidence supporting the view that SAR does not operate against virus replication (Balazs *et al*., 1977: tobacco-TMV; Fraser *et al.*, 1979: *Nicotiana glutinosa*-TMV; Sziraki *et al*., 1980: tobacco-TMV; Coutts and Wagih, 1983: cowpea- and cucumber-TNV; Pennazio *et al*., 1983: tobacco-TNV; Pennazio and Roggero, 1991b: asparagus bean-TNV; Pennazio and Roggero, 1991c: soybean-TNV). These results, however, are seldom quoted and discussed in the more recent papers or reviews concerning SAR.

What is the target of SAR? If SAR limits cell-to-cell virus spread, movement proteins (MPs) may be involved. It is known that spread of infectivity from the initiation site *via* plasmodesmata is mediated through virus-encoded MPs (Wolf and Lucas, 1994). If spread is impeded following SAR induction (as logically deducible from the reduction in lesion size), the accumulation of MPs might be impaired. In fact, during the development of HR in tobacco inoculated with TMV, MP accumulation proceeds actively till the appearance of lesions, then suddenly stops (Moser *et al*., 1988). This finding is the first experimental evidence of a molecular mechanism of virus localization, supported by much other evidence based on different experimental approaches (for references, see Pennazio, 1991). Obviously if SAR prevents virus replication as well as spread, an additional mechanism must be involved.

What is the mechanism that restricts lesion size? Does it involve a more rapid collapse and death of cells? The answers to these questions can be only speculative and HR may be useful again.

Cell collapse occurs some hours before necrosis as a consequence of membrane impairment and damage (Goodman and Novacky, 1994), owing to activation of an oxidative burst (Sutherland, 1991; Bolwell and Wojtaszek, 1997). Activation of an oxidative burst is the result of rapid signalling between plant and pathogen, and causes changes of membrane permeability and probably stimulation of gene expression (Yang *et al*., 1997). Oxidative burst and generation of reactive oxygen species (ROS) have been explained by a model involving a system activated by HR, producing hydrogen peroxide (Levine *et al*., 1994).

As already discussed, systemic resistant tissues accumulate SA, some of which is in an inert glucosylated form (Enyedi *et al*., 1992; Malamy *et al*., 1992; Shulaev *et al.*, 1995; Lee and Raskin, 1998). In fact, too high endogenous SA concentrations should result in chlorotic or necrotic symptoms (Takahashi *et al*., 1997), whereas resistant tissues never show visible or ultrastructural alterations (see Martelli, 1980). After challenge inoculation, the inert form of SA may more rapidly release free SA, whether or not SA really blocks catalase activity (Chen *et al*., 1993; Takahashi *et al*., 1997). Catalase scavenges hydrogen peroxide and toxic amount of it should rapidly accumulate and reinforce ROS production induced by the challenging HR. More rapid necrosis might therefore occur, with consequent impairment of cellular processes including synthesis of MPs. Thus SAR should operate by accelerating HR, *i.e.* by enhanc-

ing the localizing mechanism. This view, has already been suggested by van Loon (1983) and Fraser (1985), and re-proposed by Pennazio (1991) and van Loon (1997). The mechanism here suggested is oversimplified, but not inconsistent with experimental results.

Another interesting possibility has been suggested by Fodor *et al.* (1997). The oxidative burst produced during the HR of tobacco to TMV should activate genes encoding for antioxidative enzymes which might protect plant tissues from lipid peroxidation around the infection site, so preventing enlargement of the necrotic lesions. According to this mechanism, SA should not play any role. A similar hypothesis had been expressed by Sziraki *et al.*, (1980) for a putative role of cytokinins in tobacco hypersensitive to TMV and, more recently, re-proposed by Beckman and Ingram (1994) for the hypersensitive response of potato to *Phytophthora infestans*.

SAR AGAINST SYSTEMIC VIRUS INFECTION. Localized virus infection is a very useful model to investigate HR and SAR. In Nature, however, this type of infection is practically unknown and HR can be considered a form of extreme resistance. Virus diseases are produced only as a consequence of systemic infection, and this should be the object of any practical study of resistance.

It is generally held that SAR defends plants against all types of pathogen including viruses which infect systemically. Does SAR really operate against systemic virus infection? Surprisingly the subject has received little attention. However, this neglect is certainly not the fruit of indifference but rather a perfect choice (it is impossible to investigate something that does not exist).

The results published on SAR against systemic virus infection have been negative both as regards virus replication and viral pathogenesis (Fraser, 1979: tobacco-TMV; Pennazio and Roggero, 1988: tobacco-TMV, -potato Y potyvirus (PVY), necrotic strain, -tobacco rattle tobravirus (TRV); Ye *et al.*, 1990: tobacco-TMV; Pennazio and Roggero, 1991b: asparagus bean-cucumber mosaic cucumovirus (CMV); Pennazio and Roggero, 1991c: soybean-alfalfa mosaic alfamovirus, -CMV, -soybean mosaic potyvirus). As far as we know, only two papers have reported positive results: (*i*) van Loon and Dijkstra (1976) reported that TNV localized infection reduced TMV replication in non N gene-containing tobacco. The amount of TMV in resistant and control systemically resistant leaves was 17 µg and 21 µg, respectively, *i.e.* 19% reduction. Virus content was determined spectrophotometrically on purified leaf extracts in only one assay, and we suggest that further repetitions should have been done to clearly demonstrate an effect of SAR on TMV; (*ii*) Bergstrom *et al.* (1982) described a form of resistance, induced in cucumber by TNV, which delayed the appearance of systemic symptoms produced by challenging CMV inoculation. Some days later, however, severe symptoms reappeared.

CONCLUDING REMARKS

We think it misleading to make statements such as: '*SAR is a general response developed by plants against various invaders, even if many important questions remain',* but such pronouncements commonly preface most papers and reviews on this subject, without clearly explaining the unreliability of SAR in protecting plants against systemic virus infection. Kuc (1982) has argued that plant susceptibility should not depend on the absence of appropriate genetic information for resistance but on the absence of systems activating such information. Kuc (1987) later suggested that susceptibility and resistance are not properties separated by a genetic barrier but are arbitrary points along a continuum of effects produced by biotic or abiotic stresses. This means that a susceptible plant would have an inherent capacity to respond to a given pathogen, if appropriately stimulated to produce resistance.

Plant virologists know that each plant species has the genetic and biochemical apparatus necessary to produce HR against at least one virus. Can SAR change a susceptible into a hypersensitive response? We think this is a very complicated question, and to answer it, the mechanism of HR must be elucidated. HR requires a high level of specificity to be activated. Dawson *et al.* (1988) and Culver and Dawson (1990) have shown that tobacco plants susceptible to TMV can respond hypersensitively only if the virus has an aberrant coat protein. A single amino acid substitution in the virus-encoded replicase of tomato mosaic tobamovirus renders the mutant unable to replicate in tomato cells whereas it replicates normally in tobacco cells (Hamamoto *et al.*, 1997). Data presented by Culver *et al.* (1994) indicates that fine details involving the stability of the quaternary structure of TMV coat protein are necessary for host cell recognition and HR elicitation by the N' gene of *N. sylvestris.* Inoculation of SA-treated tobacco plants with viruses which infect systemically resulted in HR against TRV and AMV but not against potato X potexvirus, PVY and TMV (Roggero and Pennazio, 1988), suggesting specificity of elicitation at the virus level.

Profitable subjects for future investigation would be (*i*) recognition signals and molecular manipulation of signal transduction processes and (*ii*) induction of resistance through stimulation by well defined chemical

compounds (see Ye *et al*., 1995). But first of all it needs to demonstrate that SAR is a real practical method for controlling virus diseases.

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