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What's Old and What's New in Concepts of Induced Systemic Resistance in Plants, and its Application

Joseph Kuć

2.1 Historical Perspective

Disease and induced resistance to disease in plants and animals has been with us as long as plants, animals, and their pathogens have coevolved. Observations of induced resistance in plants were reported as early as the late 1800s and early 1900s (Beauverie, 1901; Ray, 1901; Chester, 1933). Muller and Borger (1940) described carefully conducted experiments which established the phenomenon of induced local resistance (ILR) in potatoes to late blight (*Phytophthora infestans*). Inoculation of potato tubers with cultivar-nonpathogenic races of the fungus induced local resistance to cultivar-pathogenic races. This work, and subsequent studies by Muller and coworkers also established the concept of active defense for resistance, a response after infection, and this proved to be the foundation for work with phytoalexins.

Induced systemic resistance (ISR) was analytically established by Kuć et al. (1959) and Ross (1966). Kuć et al. (1959) and Maclennan et al. (1963) demonstrated that apple plants were made systemically resistant to apple scab (*Venturia inaequalis*) by infiltrating lower leaves with D-phenylalanine, D-alanine and aminoisobutyric acid (AIB). The amino acids did not inhibit the growth of *V. inaequalis in vitro* at concentrations used for infusion. Ross (1966) and coworkers demonstrated that inoculation of lower leaves of tobacco with a local lesion strain of tobacco mosaic virus (TMV) systemically enhanced resistance to the same strain of the virus. They also established the time required between induction and inoculation for ISR and its persistence. The continued research by Kuć and coworkers verified the reports by Ross and expanded and defined our understanding of ISR and its application for disease control in the greenhouse and field. They demonstrated that ISR was not specific with respect to the nature of the inducer or the biological spectrum of the diseases it protects against. Thus, unrelated fungi, bacteria, viruses, or chemicals induced resistance systemically

against all three classes of pathogens (bacteria, fungi, and viruses), and in some experiments, even protected plants against damage caused by herbicides and oxidants (Kuć, 1982, 1995a, 1995b, 1997, 1999; Dalisay and Kuć, 1995a, 1995b; Fought and Kuć, 1996; Gottstein and Kuć, 1989; Karban and Kuć, 1999; Lusso and Kuć, 1999; Mucharromah and Kuć, 1991; Strobel and Kuć, 1995). ISR was demonstrated with different plants, including cucumber, watermelon, muskmelon, tobacco, tomato, green bean, apple and pear, and was found to be effective in these plants against bacterial, fungal, and viral pathogens. An important aspect of ISR established by this body of work is that it sensitizes (or primes) plants to respond rapidly to a pathogen after infection. The molecular basis for sensitization is still unclear, but it appears that the phenomenon is even more important for defense against disease than the initial accumulation of defensive compounds, observed upon induction of systemic resistance (Kuć, 1984, 2001; Conrath et al., 2001).

Research with ISR has expanded rapidly, with contributions from many laboratories worldwide. ISR has now been reported in plants as diverse as *Arabidopsis thaliana* to coffee, and ISR is also effective against insects and nematodes (Agrawal et al., 1999; Schmidt and Huber, 2002; Hammerschmidt and Kuć, 1995).

A key to the evolution of ISR was the early research with phytoalexins, pioneered by Cruickshank, Kuć, Uritani, Tomiyama, and Metilitskii and their coworkers (reviewed in Kuć, 1995a; Hammerschmidt, 1999). The research with phytoalexins assigned chemical structures to the putative defense compounds and established a close relationship between the localized early accumulation of phytoalexins and inhibition of pathogen development and disease. The research also established that phytoalexin accumulation was elicited by simple inorganic and organic chemicals, as well as by microorganisms and their products. Phytoalexins accumulated in resistant as well as susceptible interactions. The difference between resistant and susceptible plants was evident in the timing of phytoalexin accumulation: in resistant plants accumulation was rapid and in susceptible plants, accumulation was delayed. The early experiments conducted with phytoalexins established a foundation for ISR research, and the similarities between phytoalexin accumulation and ISR in plants are evident. Whether phytoalexins are major factors for resistance has been reviewed (Kuć, 1995a; Hammerschmidt, 1999). Most of the research with phytoalexins has indicated that their accumulation is most often associated with resistance to fungal diseases, is less so for bacterial diseases, and is unlikely to be associated with resistance to viruses, though ISR is effective against some viral diseases.

The discovery of the central role of salicylic acid (SA) in some mechanisms for ISR opened the door to investigations of the regulation of, and mechanisms involved in, ISR on a molecular and genetic level (Metraux, 2001).

2.2 The Phenomenon of Induced Resistance

Pertinent to an understanding of the phenomenon if ISR is a consideration of the question about why plants and animals are susceptible to infectious diseases. Disease resistance in plants and animals requires multiple components (see

Section 2.3). The antibody-based, or humoral, immune system in animals is highly specific, both in terms of the elicitors (specific antigens) that generate a humoral response, and in the nature of the response (the production of antibodies that recognize and bind to the antigen). The first time an animal is exposed to an antigen, the humoral response is sluggish. Upon subsequent exposure to the antigen, the response is much more rapid and results in the production of greater quantities of antigen-specific antibodies. These antibodies work in concert with cell-mediated defense responses in animals to limit pathogen attacks.

ISR in plants lacks the specificity of the humoral immune system: ISR can be generated by a wide variety of structurally unrelated elicitors, and once activated, it is effective against a wide variety of organisms. Some plant–pathogen interactions are, however, highly specific, as is observed in gene-for-gene interactions and host specificity.

Excluding genetic faults, animals and plants express genes for resistance mechanisms, and both have demonstrated resistance to the bacteria, fungi, and viruses in their environment throughout the ages of evolution. The mechanisms by which plant and animal defense, or immune, response systems function are clearly very different, but in one principle they are similar: unless activated sufficiently in a timely manner, the responses will fail to contain a given pathogen, even when all the required components needed to contain a pathogen are present. In animals, and seemingly also in plants, immune or defense responses may fail when (1) there has been no prior exposure to the pathogen, or another elicitor, which can prime the immune system to produce a more rapid and effective response, (2) the plant or animal is subjected to stresses (e.g., poor nutrition, developmental or environmental stress) which decrease its ability to mount an immune or defense reaction, or (3) the pathogen dose is too high and defenses, while activated, are simply inadequate to deal with the number of infectious agents. To use our species as an example, human disease epidemics have occurred in the past when groups of people were exposed to novel pathogens they had never encountered before (e.g., smallpox, new strains of influenza), or when changes in human living conditions or the environment brought people into contact with greater numbers of pathogens (e.g., bubonic plague), and it is commonly observed that the malnourished, the elderly, and the very young tend to be more susceptible to diseases than healthy adults. Genetic variation between individuals also exists, and some human immune systems are simply more effective at dealing with pathogens than others.

In plants, particularly in natural communities of plants, their defense responses are extremely effective at combating pathogens. To my knowledge, a plant species has not disappeared from the earth as a result of disease, unless human activity can be considered a disease. However, plants that survive diseases in the wild are not necessarily perfectly fit, lush, and healthy. A disease-tolerant plant may be able to fulfill its evolutionary prerogative and reproduce, and is in terms of evolution a success; but unless the quality and yield of produce from the plant is high, this plant is not useful to current agricultural production. A distinction should be made between disease resistance needed for the survival of a species, and disease resistance necessary to minimize economic losses when growing the

plants commercially. When we speak of the need to increase plant resistance to disease, we are actually referring to the latter, since plants in natural communities already have the defenses they need to survive.

2.3 Single and Multigenic Resistance, ISR and Defense Compounds

The literature contains references to many defense compounds and their alleged importance in plant disease resistance. However, nounequivocal case has been made for the necessity of any one defense compound for resistance, and many compounds accumulate after infection. More information is necessary concerning the contribution of defense compounds to resistance, individually and collectively, as well as the timing, magnitude, and localization of their accumulation relative to pathogen development. More research is also necessary to determine the mode of action of defense compounds, whether they inhibit development of a pathogen and/or reduce damage caused by a pathogen, and whether there is an interdependence or synergy in their activity. Until this information is available, the reported defense compounds are at best associated with resistance and are putative defense compounds/mechanisms (PDCM).

The PDCM include those that are preformed, as well as those that are produced in response to wounding, and those that accumulate locally or systemically after infection, ISR, or infection after ISR. PDCM include simple inorganic and organic compounds, peptides, proteins, enzymes, and phenolic and carbohydrate polymers (Table 2.1). It is evident, therefore, that many different pathways, loci, and compartments are involved in their synthesis and different mechanisms are required for the regulation of their accumulation and mode of action. As important as activation of resistance mechanisms is to disease resistance, it is equally vital to the plant's survival that the regulated, though apparently chaotic, metabolic processes that were put into motion can be redirected to normal.

From the above it seems reasonable to conclude that the mechanisms for ISR and disease resistance/susceptibility are multicomponent and, therefore, their regulation will be multicomponent. Since the genes for PDCM are present in susceptible and resistant plants, what is it that regulates single gene resistance, and its frequent loss, as well as multigenic resistance and ISR?

TABLE 2.1. Putative defense compounds/systems for disease resistance in plants

Passive and/or wound responses
Waxes, cutin, phenolic glycosides, phenols, quinones, steroid glycoalkaloids, suberin, terpenoids and proteins
Increases after infection
Phytoalexins, reactive oxygen species/free radicals, calcium, silicon/silicates, polyphenoloxidases, peroxidases, phenolic cross-linked cell wall polymers, hydroxyproline and glycine-rich glycoproteins, thionins, antimicrobial proteins and peptides, chitinases, β-1,3-glucanases, ribonucleases, proteases, callose, lignin, lipoxygenases and phospholipases

Evidence is not available, and it is highly unlikely, that single gene resistance is due to the production of a single PDCM. The response of a plant with single gene resistance to a pathogen is multicomponent, and differs from the susceptible plant lacking the gene for resistance only in the timing of the response. The magnitude of response is often greater in the susceptible plant lacking the gene, but the response is delayed until after the pathogen has been established. Regardless of the presence of single gene or multigenic resistance, many unrelated organisms and chemicals can elicit the same metabolic responses in a plant and elicit ISR to a broad spectrum of pathogens and environmental stresses.

One interpretation of the above observations is that the resistance gene, via its product, regulates the timing of the expression of multiple mechanisms, either directly or indirectly, via a master switch(es), which eventually leads to the multistep mechanisms for the synthesis and accumulation of PDCM. It is likely that a master switch(es) would regulate many other switches, or cascades, which activate or deactivate signals for individual pathways and their interaction. Thus, it is important to differentiate resistance genes which regulate expression of a master switch(es) from the genes for steps within the pathways for the synthesis of PDCM.

When resistance is "lost" in a plant with single gene resistance, it is not the gene itself which is lost. What is lost is the gene's effectiveness. The genes for the PDCM are still present, as is the potential for their activation. The pathogen overcoming single gene resistance may do so by a number of mechanisms: (1) avoid activation of the resistance gene product (or receptor), and thereby a factor is not produced to activate the master switch(es) and trigger a defense response. Pathogen avirulence gene products which do not bind to plant receptors, or which bind but do not activate or fully activate the receptor, would accomplish this, (2) a product that modifies and thereby inactivates the plant receptor, (3) a product that inactivates the master switch(es), (4) a product(s) that inactivates all or many of the pathways producing PDCM. This latter possibility is highly unlikely, given the diversity of PDCM.

With multigenic resistance, the PDCM are likely to be identical to those utilized in single gene resistance. The difference between the two types of resistance would be the presence of multiple host genes, which may encode receptors, capable of binding and detecting nonspecific pathogen products (i.e., fragments of cell wall polymers such as chitin and peptidoglycan, or other conserved structural components, such as lipopolysaccharides or flagellin). To avoid activating resistance, the pathogen would have to produce structural components that do not bind to any plant receptor (which is unlikely), or find a way to inactivate all the plant receptors, or the master switch(es). It is possible that binding of a nonspecific elicitor to a receptor results in less efficient activation of these receptors, but there are also a greater diversity of receptors. Upon encountering initial plant defense responses, cells of an invading pathogen may be damaged or lyse and release a great quantity of nonspecific elicitors (i.e., cell wall fragments), amplifying the original signal. Multigenic resistance is therefore much more difficult to overcome than single-gene resistance. If there are multiple and redundant master switches governing plant defense responses, it is possible that they do not regulate PDCM equally,

resulting in qualitative and quantitative differences in PDCM and the timing of their appearance.

Since ISR has the same PDCM as those associated with single gene and, probably, multigenic resistance, and as ISR lacks specificity with respect to the nature of the inducers and spectrum of its biological activity, it is possible that inducers of ISR, directly or indirectly, regulate a master switch(es) governing the timing of PDCM production. The factors activating a master switch(es) have yet to be fully elucidated, but could include those produced by single and multigenic resistance, i.e., reactive oxygen species (ROS). The difference between gene-based resistance and ISR would therefore be the site of action. In gene-based resistance, the expressed host receptors (resistance gene products) govern resistance. In ISR, resistance may be governed via the priming of master switch(es).

The agents causing ISR, whether microorganisms or chemicals, could affect a master switch directly by causing metabolic perturbations that generate a signal affecting that switch, i.e., ROS. During the induction of ISR in Plant A, the plant's master switch(es) are activated and PDCM are produced. A susceptible, noninduced plant (Plant B) that is infected by a pathogen could also generate ROS, activating the master switch(es) and the production of PDCM, but this response would be delayed, allowing the pathogen to spread and cause further damage. Upon subsequent infection by a pathogen in each of Plants A and B, the master switch(es) react more quickly. The difference is that Plant B has suffered greater damage and may not even have survived its first infection.

There may be many paths leading to PDCM, plant disease resistance and ISR. The key may be the levels of incompatibility/compatibility between a microorganism or chemical and the plant during the early stages of their interaction, and this may be determined by the ability to generate, tolerate, or inactivate ROS.

2.4 Induction of ISR

The inducers of ISR vary greatly and include fungi, bacteria, viruses, nematodes, insects, components, and products of pathogens and nonpathogens, organic and inorganic polymers and simple organic and inorganic compounds (Table 2.2). It is not possible to assign a unique chemical structure as being necessary for the induction of ISR (Fought and Kuć, 1996). Compounds as simple as phosphate salts and ferric chloride have been reported to induce ISR (Gottstein and Kuć, 1989; Mucharromah and Kuć, 1991; Reuveni et al., 1996, Reuveni and Reuveni, 1998; Manandhar et al., 1998). Therefore, inducers are active not because of what they are, but rather for what they do, and they are likely to have common features in how they affect plants. Not all inducers have been reported active in all plants against all diseases, but it is clear that biologically-induced ISR is active with the same microorganism as inducer in unrelated plants against unrelated diseases (Kuć, 1982; Kuć, 2001). The commercially available compound Bion (benzo(1,2,3)thiadiazole-7-carbothioic acid S-methyl ester) is active in many unrelated plants against many unrelated pathogens and some nematodes and insects (Oostendorp et al., 2001).

TABLE 2.2. Agents reported to elicit induced systemic resistance in plants

- fungi, bacteria, viruses, nematodes, insects
- fungal, bacterial and plant cell wall fractions, intercellular plant fluids and extracts of plants, fungi, yeasts, bacteria and insects
- potassium and sodium phosphates, ferric chloride, silica
- glycine, glutamic acid, α-aminobutyric acid, β-aminobutyric acid, γ-aminobutyric acid, α-aminoisobutyric acid, D-phenylalanine, D-alanine and DL tryptophan
- salicylic acid, *m*-hydroxybenzoic acid, *p*-hydroxybenzoic acid, phloroglucinol, gallic acid, isovanillic acid, vanillic acid, protocatecheic acid, syringinc acid, 1,3,5 benzene tricarboxylic acid
- D-galacturonic acid, D-glucuroinic acid, glycollate, oxalic acid and polyacrylic acid
- Oleic acid, linoleic acid, linolenic acid, arachdonic acid, eicosapentaenoic acid
- Paraquat, acifluorfen, sodium chlorate, nitric oxide, reactive oxygen species
- 2,6-dichloroisonictonic acid, benzo (1,2,3) thiadiazole-7-carbothioic acid *s*-methyl ester
- jasmonic acid, methyl jasmonate, ethylene
- ethylene diamine tetraacetic acid (EDTA), riboflavin
- probenazole and 2,2-dichcloro-3,3-di-methyl cyclopropane carboxylic acid
- -dodecyl DL-alanine and dodecyl-L-valine
- phenanthroline and ptthalocyanine metal complexes (cobalt, iron and copper)

The acceptance of the non-specificity of inducers of ISR is a key to an understanding of the mechanisms responsible for ISR and its induction and regulation. Metabolic perturbation resulting in the generation of ROS may be one feature in common amongst the great diversity of ISR inducers. Many current reports support an important role for ROS in resistance and ISR (Averyanov et al., 2000; Dempsey et al., 1999; Lamb and Dixon, 1997; McDowell and Dangl, 2000; Murphy et al., 2001; Kim et al., 2001; Kiraly, 1998).

2.5 Application of ISR

Microorganisms and chemicals that induce ISR are commercially successful and available for the control of plant diseases (Oostendorp et al., 2001; Kim et al., 2001; Zhender et al., 2001; Reuveni et al., 1996; Bednarz et al., 2002). These include such diverse agents as rhizobacteria, Bion, Messenger, inorganic phosphates, ROS, and Probenazole. The development of new commercial agents for ISR depends upon several factors, some of which are favorable for development, and some unfavorable.

Favorable factors include:

(1) Problems with the resistance of pathogens to classical pesticides.
(2) The necessity to remove some pesticides from the market, the increased testing and cost of testing to meet requirements of regulatory agencies and the lack of substitutes for removed compounds.
(3) Health and environmental problems, real and perceived, associated with pesticides and the increased popularity of "organic" crops and "sustainable agriculture."
(4) The inability of pesticides to effectively control some pathogens, e.g., virus and soilborne pathogens.

(5) Classical pesticides may not be economically feasible for farmers in developing countries. In these countries, the level of awareness for the safe and effective application of classical pesticides is low, thus creating dangers to human health and the environment.
(6) Resistance of the public to genetically modified plants. In ISR, foreign genes are not introduced. The innate genes for resistance in the plant are those that are expressed.
(7) ISR has a broad spectrum of activity and its effectiveness persists for an extended period.
(8) Since many defenses are activated, pathogens are less likely to develop resistance to ISR.

Unfavorable factors include:

(1) Some plant pathologists still scoff at the applicability of ISR.
(2) Only high profit, patented and complex inducers make the major markets. Who champions the simple, nonpatented yet equally effective compounds?
(3) Lack of sufficient information exchange and financial support for non mega-agribusiness-oriented scientists, and a lack of adequate information flow to farmers and the public.
(4) Unlike classical pesticides which directly kill or inhibit the development of a pathogen, ISR depends upon the expression of genes for resistance in the plant. Therefore ISR is more subject to physiological and environmental influences that may alter its effectiveness.
(5) Public and farmer's apprehension of new technologies.

2.6 Directions for Future Research

Priorities for research include investigations that should have and could have been completed years ago as well as those that require new information and technologies for their initiation.

Which of the putative defense compounds contribute to resistance? Is the timing of their appearance important? Is the synthesis of the compounds and the timing of their appearance regulated differently? More attention should be given to individual plant–pathogen interactions to determine which inducers and their doses, as well as which putative defense compounds and the timing of their appearance, are important.

Do plants respond to the pathogen per se or to the stress (metabolic perturbation) caused by the pathogen, or a combination of both? What is the translocated signal(s) in ISR? What causes the synthesis or release of the signal(s)?

Is it possible to develop plants with enhanced ISR through plant breeding? When breeding for resistance, are we also often breeding for enhanced ISR? What are the genetic and metabolic bases for the cascade of events associated with defense compounds, ISR, and sensitization (priming)?

What are the molecular and practical significances of the nonspecificity of the agents which elicit ISR?

Are the mechanisms for the different types of resistance (nonhost, agerelated, organ specific) the same or different, and do they have components in common with ISR? Can the genes for the different types of resistance be selectively expressed without detrimentally influencing plant development, e.g., express genes for age-related resistance without prematurely aging the plant?

What are the roles of oxidative stress, ROS, and nitric oxide as defenses against disease and initiators of defense mechanisms? In mammals, hydrogen peroxide and superoxide anion are the major microbiocides produced by circulating phagocytic leukocytes. However, hydrogen peroxide and ROS may function alone or together with NO to enhance death of pathogens, as well as triggering transcriptional activation of plant defense genes and the hypersensitive response (Delledone et al., 1998). Elevated levels of Ca^{2+} can enhance NO synthase activity, and perhaps this partially explains the frequent association of calcium with resistance. Averyanov and colleagues (2000) reported that phenanthroline and phthalocyanine metal complexes induced ISR to rice blast when applied to foliage or the soil. Both compounds produced ROS, and the authors suggest that increased ROS resulted in ISR, sensitization, and the hypersensitive response. In addition, metal complexes of phthalocyanine stimulated ISR when applied to rice seeds before sowing, and the protection lasted for at least one month in seedlings. More emphasis should be placed on effective seed treatments for ISR.

Can defensins and protegrins be utilized effectively for ISR? Defensins and protegrins are antimicrobial peptides found in plants and animals ranging from insects to humans. They are part of an innate immune system which evolved before antibodies and lymphocytes. Since antimicrobial peptides are reported in plants, ISR may provide a mechanism to enhance production of the peptides in plants without the introduction of foreign genes.

Do DNA-binding proteins (zinc fingers) and cell-permeable polyamides have a role as agents for the selective expression of genes for ISR? Synthetic transcription factors have been developed which are designed proteins containing DNA-binding elements, or zinc fingers (Borman, 2000). Similar structures are found in some natural transcription factors. Zinc fingers are independently folding domains of about 30 amino acid residues centered on a zinc ion. These proteins and synthetic polyamides can turn endogenous genes on and off in living cells in a very specific manner.

Does the progress made with bacterial harpin indicate the presence of many similar proteins for ISR? Harpin produced by the pathogenic bacterium responsible for fire blight (*Erwinia amylovora*), induces systemic resistance in plants against many diseases caused by fungi, bacteria, and viruses, as well as some insects (Brasher, 2000; Bednarz et al., 2002). It also promotes root growth, reducing the need for water. The protein can be sprayed on plants before they are attacked by pathogens and it degrades so quickly that it cannot be detected within two hours of application. Other pathogens and even some nonpathogens are reported to produce harpin-like proteins and it is likely that proteins other than harpins have a capability for ISR.

2.7 Conclusions

Though resistance and susceptibility to pathogens are often specific and biochemicals determining this specificity have specific structures and receptors, nonspecific agents and multiple signals and pathways for their transduction can also induce resistance to unrelated pathogens and toxicants. This makes the possibility of finding additional effective agents for ISR and disease control highly promising. The agents need not be patented, expensive, or complex. Much more research is needed on the use of ISR agents to reduce dependence on chemical pesticides and enhance utilization of high-yielding plants that presently have a level of resistance that is inadequate for disease control under high pathogen pressure. ISR does not depend upon introducing genes into the plants, and it would not meet the resistance from the public engendered by genetically modified plants. ISR should be increasingly incorporated into integrated pest management practices. Increased funding and information exchange is needed to better utilize and direct the rapidly emerging information concerning signals, receptors, signal transduction, and gene expression for the practical control of plant disease.

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