

## INTEGRATING BIOLOGICAL STRATEGIES TO CONTROL DISEASE IN INTENSIVE AGRICULTURE

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**Summary.** Societal concerns about pesticide residues in food and the adverse effect of pesticides on the environment, combined with the increasing costs of petro-chemical derived pesticides, are factors influencing the development of alternative disease control strategies. The ban on methyl bromide and copper-based fungicides is also a factor. Soil-borne diseases are difficult to control in intensive agriculture and have been the primary target for biological control in the past. There are a number of PGPR and *Trichoderma* formulations in commercial use. The active organisms have been selected for their antagonism of soil borne pathogens and, in the case of PGPR, for plant growth promotion. More recently, the potential of root inoculants (both PGPR and AMF) to prime plant defences, that is, their ability to induce systemic resistance, has been investigated in parallel with the development of 'plant activators' which also induce host resistance. It has been hypothesised that exploitation of antagonism, combined with priming and activation of plant defences by chemical sprays, may result in an holistic strategy for controlling both soil- and air-borne plant pathogens. Fungicides, however, will be difficult to replace. They are relatively inexpensive compared with inoculants and chemical activators. They are broad spectrum and problems of resistance can be addressed by sequential use of chemical with different modes of action. Dosages can be reduced by using precision application based on accurate disease forecasting. Biological alternatives on the other hand, face problems of competition in soils with microbial diversity. Furthermore, constitutive resistance has been reduced with the domestication of crops and the effect of the environment (nitrogen supply, water availability etc.) on the ability of the plant to sustain the burden

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of induced resistance, and the production of a variable array of respiratory and other inhibitors by different pathogens, mitigate against the efficacy of induced resistance. With no immediate prospect of durable resistance to pathogens emerging from genetic engineering, other than possibly viruses, it is likely that fungicides will continue to provide, with traditional breeding for resistance, the main protection against plant diseases.

**Keywords:** arbuscular mycorrhizal fungi, induced resistance, plant activators, plant growth promoting rhizobacteria, plant priming.

**Abbreviations:** AMF- arbuscular mycorrhizal fungi, ISR- induced systemic resistance, JA- jasmonic acid, PGPR- plant growth promoting rhizobacteria, SA- salicylic acid.

## INTRODUCTION

Prior to the 19<sup>th</sup> century, agriculture was very labour (human and animal) intensive and the main, if not the only regular input, was the planting material (Chrispeels and Sadava, 2003). It depended on diverse land races, poly-cropping (poly-varietal cultivation, inter-cropping, alley-cropping) and crop rotation to control disease (Thurston, 1992). Soil fertility was maintained by the cultivation of nitrogen-fixing crops in rotation or in poly-cropping, by employing long fallow periods or by returning the land to pasture. Soil fertility was also increased by collection of biological material from the wild, where available. Importantly, cultivated areas were bordered by natural vegetation, which acted as a reservoir for predators of pests ('refugia') (Altieri, 1995). These systems were sustainable and in some regions e.g. the Altiplano (high Andean plains), are still the main sources of food for the indigenous populations. Traditional systems represent the results of trial and error over millennia and have been defined by Altieri (loc. cit.) as 'the result of the co-evolution of local social and environmental systems and that exhibit a high level of ecological rationale expressed through the intensive use of local knowledge and natural resources, including the management of agro-biodiversity in the form of diversified agricultural systems'. Traditional farming persists in many areas in Central and South America and in the Far East. In summary, traditional agriculture (low input/low output) is based on a holistic approach, which involves the cultivation of landraces within a managed ecosystem.

In the early 19<sup>th</sup> century, agriculture underwent a revolutionary change in the industrialized world, with a reduction in labour to approximately 10% of that traditionally employed, reflecting mechanisation and development of off-farm processing and markets. Production was not significantly affected. By the 1980s, labour had been further reduced to 1% of that of the 18<sup>th</sup> century, crop yield had increased many-fold but so had the inputs with more mechanisation, the use of fertilizers,

pesticides and irrigation (Chispeels and Sadava, 2003). Behind the increased productivity was the driving force of plant breeding, which, from the 1960s to the present, has resulted in large increases in crop yield for major world crops e.g. the cereals (the 'Green Revolution'; see Conway, 1997). This yield increase has, however, depended on increased inputs of fertilisers, pesticides and increase in the practice of irrigation (Chispeels and Sadava, loc cit.). The breeding of high-yielding varieties with good organoleptic characteristics and processing qualities has led to a narrowing of the genetic diversity in crops, which resulted in a reduced competitiveness with weed species and decreased resistance to pests and diseases that created the requirement for pesticides.

Crop production in intensive agriculture is herbicide-dependent and is predominantly focussed on the cultivation of high-yielding varieties, with the use of insecticides and fungicides taking precedence over the exploitation of genetic resistance for pest and disease control in some crops (NIAB, 1982). Heavy selection pressure in large-scale monocultures in the absence of refugia for antagonists of airborne pests and pathogens, has led to the emergence of resistance to site-specific pesticides and the persistence of resistant organisms (Russell, 1995). Fungicide resistance has been combated by the strategic deployment of fungicides with different modes of action. Soil fertility, both in terms of species diversity and population sizes, is also reduced in high input soils, e.g. AMF, which are inhibited by high applications of phosphate, may be absent from agricultural soils (Whipps, 2004). Crop rotation, a traditional method to reduce the inoculum of soil borne diseases, is less effective in intensive agriculture.

The market forces which are driving the search for alternatives to fungicides are the rising costs of fossil-fuel based pesticides; consumer resistance to pesticide residues in food, and the adverse environmental impact of pesticides. Some very effective chemicals, such as organo-mercurial pesticides, the soil sterilant methyl bromide and copper-based fungicides used mainly by organic growers, have been banned or are in the process of being phased out on safety grounds (Ghorbani et al., 2005). The search for alternatives to fungicides originated with investigations of suppressive soils – soils in which the pathogen was present but no disease occurred - and with the isolation of disease-suppressive plant growth promoting rhizobacteria (PGPR; Bashan, 1998). PGPR have been evaluated with varying levels of commercial success for the control of soil borne pathogens but it has also been shown that they, biotic and abiotic stresses, and components of fungal and bacterial metabolism ('elicitors') may prime ('potentiate') plant defences against airborne pathogens. More recently, analogues of pathogen stress signalling compounds have been formulated for spray application to activate plant resistance pathways (Oostendorp et al., 2001). Here, plant resistance will be described and methods to exploit pathogen antagonism and induced host resistant in disease control will be discussed.

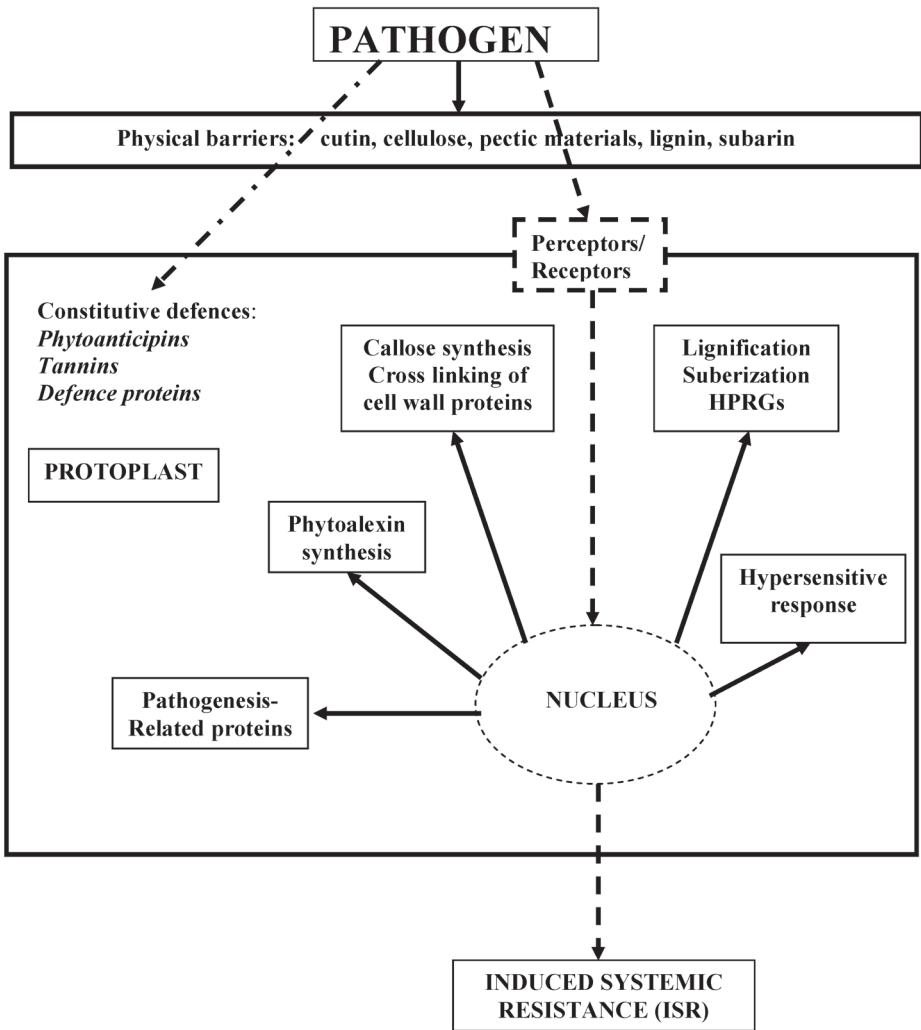
## Plant resistance to pathogens

Briefly, wild or weakly domesticated plants are resistant, termed 'non-host resistance' (NHR), to in excess of 100,000 characterised crop pests and diseases (Heath, 2000). Non-host resistance consists of two components, constitutive resistance and induced resistance (Dickinson, 2003; Strange, 2003). Constitutive resistance is based on pre-formed physical barriers including materials such as cutin and lignin which many pathogens cannot hydrolyse; inhibitory compounds (phytoanticipins), tannins and inhibitory proteins (Fig. 1). Induced resistance is based on the up-regulation of, or de novo production of, inhibitory compounds (phytoalexins), pathogenesis-related proteins (proteins which have characterised or have putative roles in directly combating pathogens such as chitinases), and other stress-related compatible solutes and protective proteins (Fig. 1; Vidhyasekaran, 2002). The latter solutes and proteins also protect against stresses associated with pathogenesis such as oxidative stresses and drought stresses.

In breeding for yield; processing characteristics (breeding for low tannins); palatability (e.g., thinner cell wall, although this may also be a consequence of high nitrogen application), and food safety (e.g., selection for low glucosinolate accumulation), plant breeders have weakened the constitutive defences of domesticated plants. Indeed, in many crops cases, lack of resistance to specific pathogens has led to breeding programmes for resistance. In most cases this is based on major gene resistance (the variety is either resistant or susceptible) (Chisholm et al., 2006) and to a lesser extent on polygenic resistance (where the variety shows quantitative resistance).

## Control of soil borne diseases

In addition to the basic aspects of site selection, site preparation including drainage and selection of an appropriate planting date, control of soil borne diseases is largely centred on the control of pathogen inoculum through seed certification, seed sterilization and rotations. For high value crops, seedbed sterilization with methyl bromide (see above) was cost effective. Fungicide seed coatings and root dips are also used. The use of fungicides to control soil diseases is problematic (Domsch, 1964). Crop rotation is effective for non-native soil pathogens. In traditional agriculture fallow periods were included in rotations. However, in some regions e.g. in northern Europe, fallow periods are too costly and long rotations are problematic due to the lack of markets for alternatives to cereals and potatoes. Consequently, rotations may not be long enough to optimise the benefits. Continuous cropping can lead, as with take-all decline in cereals, to the build up of antagonists of pathogens in soils but again this may take too long to be practical in commercial production (Rowe, 1993).



**Fig. 1.** Representation of constitutive and induced defences against pathogens. When the pathogen breaches the physical barriers they encounter antimicrobial compounds (metabolites and macromolecules). Pathogen attack may also be detected by receptors and/or perceived by changes in membrane fluidity, which signal the induction of host responses.

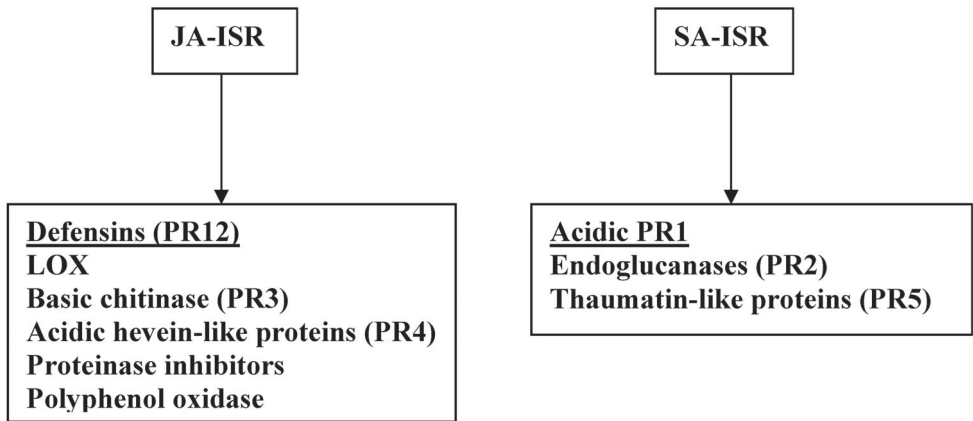
There are several biological control strategies for the control of soil borne diseases. These involve either attempt to increase soil antagonism to pathogens (Gamliel et al., 2000) or to protect the rhizosphere by the use of inoculants (Compant et al., 2005). In organic farming there is much emphasis on increasing soil fertility by the application of organic material, which can result in pathogen suppression (Gamliel et al., 2000). Increasing soil fertility may also reduce the efficacy of biological in-

oculants whose niches may be reduced (Hoitink and Boehm, 1999). Inoculants such as *Trichoderma* spp. (Jensen and Wolffechele, 1995), PGPR (Compant et al., 2005) and AMF (Whipps, 2004) have been the subject of very considerable research effort and many have been shown to control disease under experimental conditions in the laboratory or greenhouse but few have been ultimately been commercialised for use in intensive agriculture (Fravel, 2005) (see comment above re use in organic farming). Extensive trials of PGPR and AMF singly and in multiple combinations have yielded variable results (Vestberg et al., 2004). This inconsistency in commercial trials is generally attributed to environmental variability, particularly in soil type, nutrient and biological status. Some inoculants may promote plant growth thereby improving the plants ability to combat disease. These may do so by combining pathogen antagonism based on the production of characterised antibiotics, with plant growth promotion through the production of plant growth regulating compounds and provide nutrient by breaking down organic matter and solubilising phosphate.

### **Manipulation of inducible plant responses**

Induced resistance was first detected in tobacco plants following local lesion development (now referred to as hypersensitivity) where in a second or challenge inoculation with the virus, lesion numbers were reduced both in number and size. Subsequently, many abiotic and biotic stresses were shown to reduce the severity of attack by a second pathogen compared with non-inoculated controls. Induced resistance was associated with the appearance of 'novel' ('pathogenesis-related') proteins in the resistant tissues (Van Loon et al., 2006). Some of the 'novel' proteins were shown to have antifungal and antibacterial activity, and a mechanism of viral antagonism (RNA interference) was also discovered (Strange, 2003). The response to necrotising pathogens was shown to involve salicylate signalling and the induction of pathogenesis-related protein PR1a. The latter protein, or its mRNA, is used as a biomarker for this response (Fig. 2; Maleck et al., 2003).

It was subsequently shown that root inoculation with some PGPR and AMF isolates resulted in induced resistance to foliar pathogens by a pathway, which did not involve the expression of PR1a (Pieterse et al., 2001) but was characterised by the up-regulation of jasmonate-regulated proteins of PR family 12 (Fig. 2; defensins; Bart et al., 2002). The latter are used as biomarkers for this response. In parallel, it has been shown that a range of pathogen-derived metabolites, reactive oxygen species etc. can induce resistance to pathogens. Furthermore, some of these compounds e.g. chitosans, are reported to activate both SAR (Agrawal et al., 2002) and phytoalexin synthesis (Aziz et al., 2006). Unfortunately, most of the studies have focussed on protein changes in ISR or SAR and information on related changes in phytoalexins is lacking (Glombitza et al., 2004). DNA micro-array and proteomic studies have shown that the stress response is broader than activation of the SAR or ISR

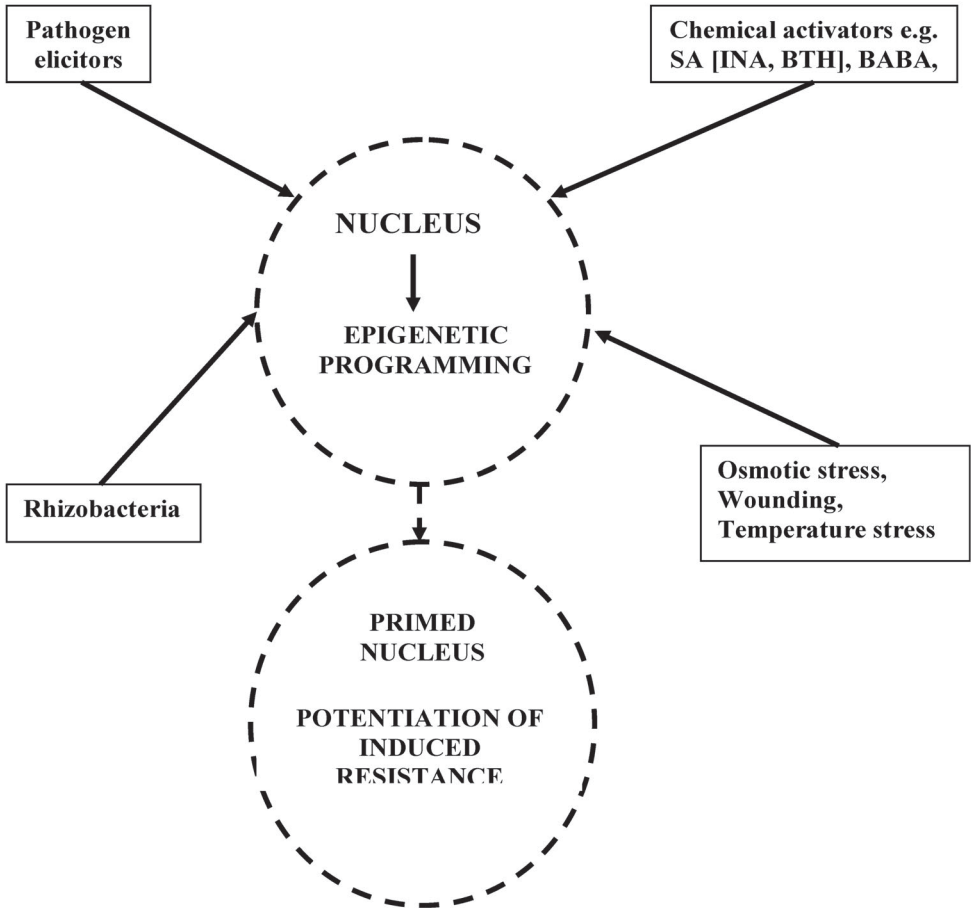


**Fig. 2.** Markers (underlined) and other proteins associated with the salicylate and jasmonate signalled defence pathways.

pathways, with hundreds of genes being up and down regulated, with some overlap in the genes affected across different stresses (Hammond-Kosack and Parker, 2003). It has been proposed that the term SAR should be dropped in favour of SA-ISR; and that ISR be referred to as JA-ISR (Tuzun, 2006).

Advances in the understanding of signalling of the plant pathogen stress response have led to the development of ‘plant activators’, that is, spray formulations of SA and SA analogues as an alternative to fungicides for the control of plant diseases (Kohler et al., 2002). The principle is that, whereas fungicides attack the pathogen directly, plant activators induce host resistance by acting as signalling compounds. The plant genotype-dependent -SA response results in the accumulation of PR1a and related proteins in ca. 5 days after spray application, the proteins decline after a few weeks. To achieve protection, the sprays are repeated to maintain the constitutive levels of the defence proteins. Some products are described in Agrios (2005).

A new holistic biological strategy (Anderson et al., 2006; Vestberg and Cassells, 2007) to control both air- and soil-borne diseases is the use of inoculants, which are antibiotic producers and SA-ISR or JA-ISR inducers, to antagonise soil-borne pathogens; and, in combination with plant activators (Gatz, 1997), to protect against air-borne pathogens. In this strategy, the inoculant primes (‘bio-primers’) the respective host defence pathway(s), and the foliage is sprayed with a chemical primer to potentiate complementary defence pathways (Fig. 3; O’Herlihy et al., 2003; Vestberg and Cassells, 2007). Priming involves epigenetic memory whereby the primed response is rapidly expressed compared with expression in non-primed plants (Conrath et al., 2001). Chemical activators are sprayed repeatedly to maintain constitutive expression of the stress responses, to protect during periods of high disease risk. As with



**Fig. 3.** Cell priming (syn. potentiation). A range of molecules and physical stresses acting on the nucleus result in appropriate stress responses. The event is memorised in epigenetic programming, allowing the response to be rapidly expressed when the stress is subsequently re-encountered.

fungicides, disease forecasting should be employed to optimise the use of the activator.

### **Biological versus chemical control of plant diseases**

Mandatory ecotoxicological investigation on new pesticides; withdrawal of hazardous chemicals such as methyl bromide, copper sulphate and others; statutory monitoring of produce in the EU for banned and unapproved pesticides and for residue levels, combined with advances in precision farming, should address the major societal concerns regarding the use of pesticides in crop production (Ragsdale, 2000).



Farmers are familiar with the cost effectiveness of fungicides and with advice on strategies to avoid resistance, forecasting to time applications and precision equipment to optimise application. It is difficult to predict a major shift to alternative methods of control, except in niche areas. Control of foliar diseases in organic production represents a potential market for biological control strategies. For example, the problem of controlling late blight of potato in the absence of copper fungicides has recently been discussed and the recommendation made that there should be a move to early maturing varieties in order to avoid severe blight pressure (Finckh et al., 2006).

The problems of introducing inoculants into soils of high fertility, such as organic fields, have been mentioned above. However, inoculants may achieve host priming in the short term, e.g. if applied to the planting material, and persistence may not be required for this function as opposed to the function of soil borne disease control. An array of bio-priming strains and chemical priming agents has been characterised. Regarding the pathways to be primed, it has been hypothesised that necrotrophs are controlled by JA-ISR whereas biotrophs are controlled by SA-ISR (Glazebrook, 2005) and the appropriate primers can be selected, in theory, to control pathogens of the respective types in a crop. In practice, the situation may be more complicated than this, as recent studies suggest that pathogen responses may be customised reflecting the pathogen perception and recognition events, and the 'secondary' stress elements such as oxidative and drought stress (Mur et al., 2006).

There has been considerable discussion of the yield penalty, due to the energy demand of synthesis of stress metabolites and proteins (Dietrich and Heil, 2004), and risk of susceptibility of induced plants to pests and pathogens, other than the target of the induced resistance (Pieterse et al., 2001). Equally problematic is the effect of pathogen toxins on the energy metabolism of the host and on the induction process itself (Fig. 4; Fujita et al., 2004). These factors, which are environmentally influenced, suggest that induced resistance may not be effective against all pathogen strains (Kuc, 2001; Zhang et al., 2001).

## **DISCUSSION**

Since the early investigations of suppressive soils, biological control has attracted considerable research effort but has generated few commercial products (Fravel, 2005). Products range from single isolate inoculants to complex mixtures of inoculants and adjuvants. The rationale for some of the products appears to be that if there are a diversity of inoculants and phyto-active chemicals something is bound to work! A problem is trying to evaluate the success and failure of inoculants is that their mode(s) of action may not be specified, or they may have only been partially characterised. Fortunately, this situation is changing with the use of DNA micro-

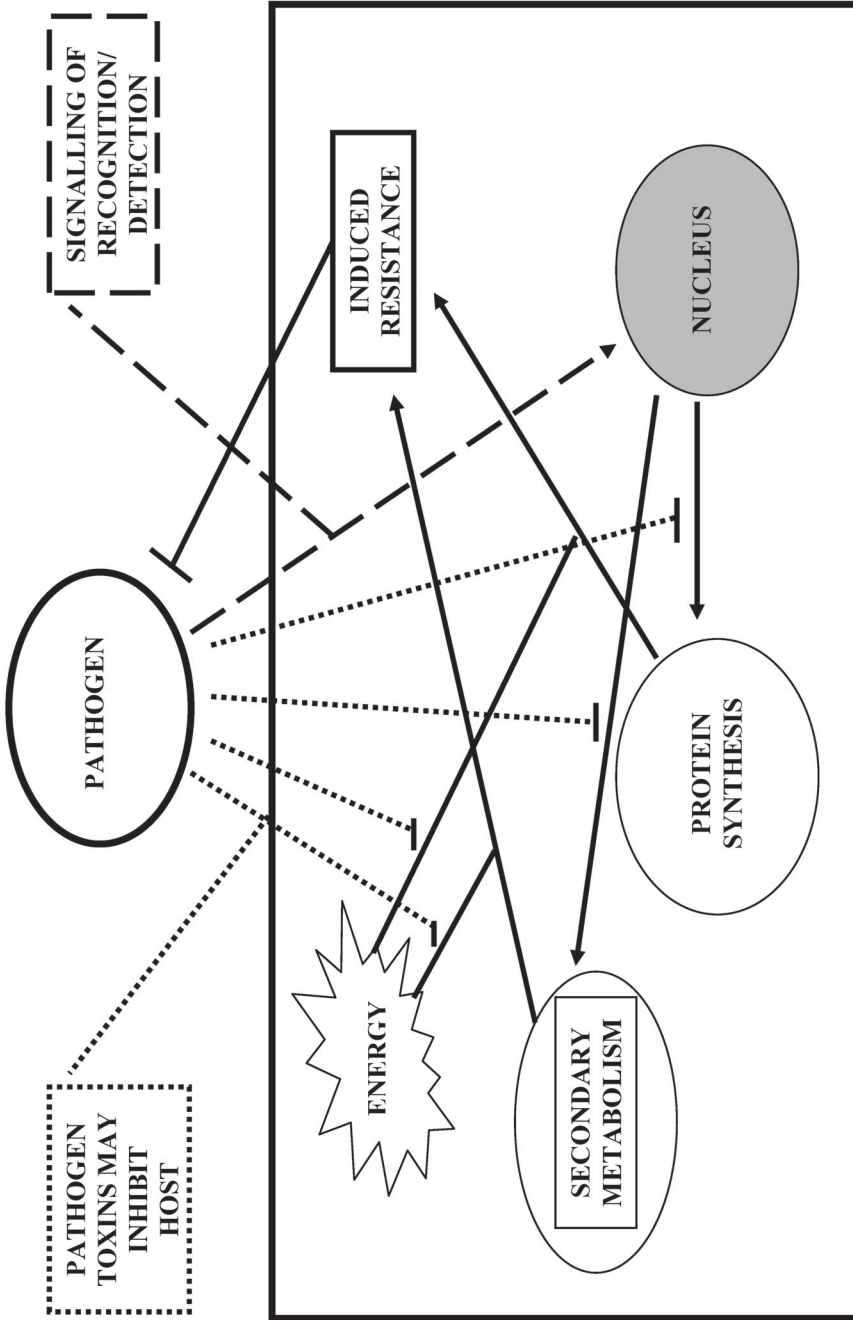


Fig. 4. A representation of pathogen-host interaction. Pathogen detection/recognition results in a stress response (see Fig. 1). Some pathogens can block the response (indicated by bars); inhibit components of the response, or inhibit the host's ability to generate the energy necessary to support the response, thereby overcoming the host.

arrays (Cheong et al., 2003) and proteomic analysis, combined with data mining software analysis of published sequences (Lee et al., 2006).

Recently, Anderson et al. (2006) have critically review the exploitation of induced plant defences in plant protection against pathogens and pests and they point out the complexity of the interactions whereby induction of resistance to one pathogen may increase susceptibility to another. Furthermore, constitutive expression of induced resistance may reduce yield (Agrawal and Karban, 1999). Another weakness in the strategy of exploiting induced resistance is that many pathogens may be able to enfeeble the host plant or inactivate the defences by the production of toxins and inhibitors (Strange, 2003) to which the plant is defenceless. The large-scale use of induced resistance may select for pathogen strains that produce such virulence factors.

Research on biological control, as on other aspects of plant pathogen-host interactions, is leading to a better understanding of the phenomena involved. The powerful new discovery tools avail to scientists will lead to even more rapid progress in dissecting biological processes (Lee et al., 2006) but can also be expected to reveal more complexity which may frustrate cost effective solutions, including application in genetic engineering for resistance (Cassells and Doyle, 2003). At the current state of knowledge, it appears that the practical application of biological inoculants and chemical plant primers and activators may, as in the past with biological control strategies, only be cost effective in niche applications.

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