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HOST-SELECTIVE TOXINS AND AVIRULENCE DETERMINANTS: What's in a Name?*

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■ **Abstract** Host-selective toxins, a group of structurally complex and chemically diverse metabolites produced by plant pathogenic strains of certain fungal species, function as essential determinants of pathogenicity or virulence. Investigations into the molecular and biochemical responses to these disease determinants reveal responses typically associated with host defense and incompatibility induced by avirulence determinants. The characteristic responses that unify these disparate disease phenotypes are numerous, yet the evidence implicating a causal relationship of these responses, whether induced by host-selective toxins or avirulence factors, in determining the consequences of the host-pathogen interaction is equivocal. This review summarizes some examples of the action of host-selective toxins to illustrate the similarity in responses with those to avirulence determinants.

INTRODUCTION

In 1905, Biffen (19) demonstrated that resistance to stripe rust in wheat was inherited in a manner consistent with Mendel's law. Shortly thereafter, Barrus (17) demonstrated that not only could different genotypes of beans display distinctly different disease responses to a strain of *Colletotrichum lindemuthianum*, but also that different strains of the pathogen could elicit different disease responses on the same genotypes of the host. By 1931, Craigie (50) had demonstrated that different "physiological races" of rust fungi could arise through sexual recombination. Thus, precedence was established that differences in either the host or the pathogen could dictate the outcome of the plant-microbe interaction. These and related studies set

the stage for Flor's historic work during the 1940s in evaluating the genetic contribution of both the host and the pathogen to the outcome of the disease interaction and the development of the gene-for-gene hypothesis (71, 72). During this same period, the first host-selective toxins (HSTs) were identified, including AK toxin in 1933 (218) and victorin in 1947 (167). These HSTs represented the first clear examples of pathogen factors that establish physiological races and whose interaction with the host could dictate specificity in the plant-microbe interaction. Thus, the discovery of HSTs coincided with a growing appreciation of the specificity of host-parasite interactions and provided the first examples of how such specificity might be determined.

HSTs are referred to as "host selective" because they are typically active only toward plants that serve as hosts for the pathogens that produce them. Currently, the production of HSTs has been documented for some 20 pathogens. They are molecules ranging from low-molecular-weight metabolites to proteins. Thus far, all of the HSTs identified are produced by fungi, and most are required for pathogenicity, such that disease does not occur in the absence of toxin production. In most cases, host sensitivity to a given HST is conditioned by a single gene, and disease does not occur in the absence of toxin sensitivity. The requirement for both toxin production by the pathogen and toxin sensitivity by the host for disease to occur provides compelling evidence that these toxins are causal to disease development. Direct molecular confirmation of this causality has been demonstrated for a number of HSTs. Obviously, as toxins, they are damaging to the plants, and it is generally held that this damage facilitates pathogenesis. Thus, HSTs have been referred to as "agents of compatibility" (231) and appear to mediate this compatibility by inducing host cell death.

In contrast to HSTs, avirulence determinants are "agents of incompatibility." These factors are the products of avirulence genes, which have long been recognized to confer incompatibility to the pathogen in the presence of the cognate resistance gene of the host. Disease occurs in the absence of either the avirulence gene or the corresponding resistance gene. Because of the requirement for expression of the avirulence gene by the pathogen and expression of the corresponding resistance gene by the host for disease resistance to occur, it is clear that avirulence determinants are causal to the disease resistance response. Direct molecular confirmation of this causality has been established in a large number of these so-called, gene-for-gene interactions. In most cases, the predominant phenotype of incompatibility is the localized death of the host, commonly referred to as the hypersensitive response (HR). The role of host cell death in resistance is an issue yet to be resolved. Nevertheless, host cell death is a typical manifestation of the resistance response.

The common association of host cell death with both susceptibility, as in diseases mediated by HSTs, and resistance, as in gene-for-gene interactions, raises the question: What is the distinction in these host responses that accounts for such obviously different outcomes of the host-pathogen interactions? This article describes a few pertinent examples of HSTs and the host responses they evoke to illustrate features in common with responses to avirulence factors. Several

excellent reviews on HSTs (156, 182, 231, 235, 260, 261) and avirulence factors (76, 140, 243) are available.

SYMPTOMS

At the simplest level of macroscopic symptom expression, a comparison of the consequences of introducing a HST or avirulence determinant into an appropriate plant, in the proper location, reveals that both evoke a cultivar-specific and rapid cell death followed by necrosis of the plant or the tissue exposed. HST activity is normally assayed by direct exposure of the plant or plant tissue to the toxin, which can be achieved by infiltration into tissue or incubation of a tissue segment or intact seedlings in a toxin solution. Similar assays can be employed for some of the characterized avirulence determinants. For example, the avirulence determinants *Avr4* (113), *Avr9* (203), and *Ecp2* (136) from *Cladosporium fulvum*, the INF1 protein of *Phytophthora parasitica* (114), the syringolide products resulting from expression of *AvrD* from *Pseudomonas syringae* pv. *tomato* (115), and the NIP1 protein from *Rhynchosporium secalis* (97, 160) all elicit a necrotic response that is macroscopically similar to that induced by most HSTs when introduced into the leaves of a genetically appropriate plant. Thus, absent the context of their primary role in disease, and based on the induced phenotypic responses, these avirulence determinants could be perceived as selective phytotoxins. Viewed from this perspective, and considering that HSTs are clearly virulence determinants, it may be informative to note that the NIP1 protein, along with NIP2 and NIP3, was originally characterized as a toxin (240, 241). NIP1 has been demonstrated to stimulate the barley plasmalemma H^+-ATPase similar to the toxin, fusicoccin (241), and is believed to function as a virulence factor in the absence of its corresponding resistance gene (160, 240, 241). Also, the Ecp2 protein from *C. fulvum* was originally demonstrated to function as a virulence factor, with mutants of *Ecp2* showing compromised colonization and reduced growth and conidiation (137). A likely role for avirulence determinants in conferring virulence in the absence of the corresponding resistance gene also has been established for a number of bacterial pathogens (76, 139, 178, 243). The majority of these bacterial determinants have been genetically identified. Attempts to evoke a response by infiltration of the direct product of avirulence genes into the appropriate plant often fail (e.g., 115, 215). The reason for the absence of a host response is beginning to be understood with an increased understanding of type III secretion systems and likely reflects a requirement for intracellular localization to initiate a response (21, 47, 77, 100, 144, 208). When these avirulence determinants are introduced into the cytosol of the appropriate plant, the recipient plant develops a necrotic response similar to that induced by most HSTs (e.g., 58, 88, 165, 221).

HOST RESPONSES

Similarities in the disease symptoms elicited by treatment with HSTs and avirulence factors suggest that the underlying biochemical mechanisms are similar.

But is this comparison superficial? Is there any evidence to indicate that these phenotypic responses share biochemical and molecular characteristics? The preponderance of evidence indicates that avirulence determinants interact directly or indirectly with the product of their cognate resistance genes to initiate signaling events that lead to the induction of the host defense response (12, 54, 157, 214, 257). Induced defense is an active response that confers disease resistance by limiting the growth and development of the pathogen. It is commonly associated with the production of reactive oxygen species (ROS), alterations in the host cell wall, accumulation of phytoalexins, expression of pathogenesis-related (PR) proteins, and localized death of host cells and tissues, typically referred to as the hypersensitive response (HR). However, despite the common association of these responses with defense, the contribution of each toward delimiting the pathogen is not well defined (98). One of the more promising approaches to understanding the complex phenotype of the resistance response is through a genetic dissection of the signaling pathways that lead to its induction. Considerable progress is being made in this regard, particularly in the "model" plant *Arabidopsis thaliana*. Research on this organism has revealed that the defense response can be mediated through a number of genetically distinguishable, but interconnected, pathways that involve the participation of signaling molecules such as salicylate, jasmonate, and ethylene (70, 86, 164). Ultimately, it should be possible to genetically isolate each of the responses associated with resistance and evaluate their contribution to the manifestation of resistance. This effort likely will establish that the contribution of each of these responses to resistance depends upon the specific plant-pathogen interaction.

At this point, the only unequivocal approach to establish that the host is expressing a resistance response is through an evaluation of the disease phenotype resulting from the combination of the host and pathogen. Even this plant inoculation approach is not without ambiguities, given that incompatibility and compatibility are judged in the context of each other and that the proliferation of the pathogen and apparent host damage during incompatibility in one interaction can approach those of compatibility in another. Because of our limited understanding of avirulence-induced resistance, and because the mode of action of most HSTs is yet to be elucidated, it may be precarious to compare their effects on the host. However, if it is accepted that expression of the various responses typically associated with defense can serve as indicators or "markers" of the resistance response, then some potentially revealing comparisons can be made. Some examples of plant responses to HSTs are described in the following sections to illustrate features shared with responses to avirulence factors.

Victorin

Perhaps similarities in responses induced by HSTs and those induced by avirulence determinants can be most clearly illustrated with Victoria blight of oats because of the genetic association of susceptibility to this disease with resistance to crown rust of oats. Victoria blight of oats is caused by the fungus *Cochliobolus*

(*Helminthosporium*) *victoriae* (166). This fungus is pathogenic strictly as a result of its ability to produce the HST, victorin (167). All isolates that produce victorin are pathogenic, whereas mutants or segregating progeny that do not produce the toxin are nonpathogenic (200). Sensitivity of oats to victorin, and thus susceptibility to the pathogen are conditioned by the dominant allele at the *Vb* locus. All dominant *Vb* genotypes are both sensitive to victorin and susceptible to the pathogen, and all homozygous recessive genotypes (*vb vb*) are toxin-insensitive and resistant. Thus, Victoria blight occurs only when a victorin-producing isolate of *C. victoriae* encounters an oat plant carrying a dominant allele at the *Vb* locus.

Victoria blight was originally described by Meehan & Murphy in 1946 (166) and found only on oat lines containing Victoria-type resistance to crown rust. The Victoria oat variety had been introduced into the USA from Uruguay for use as a source of resistance to crown rust, caused by the fungus *Puccinia coronata* (145). Crown rust resistance conferred by Victoria-type oats is due to the dominant *Pc2* gene, and the crown rust/oat interaction appears to be a classic gene-for-gene type of interaction. Despite extensive attempts to separate crown rust resistance (*Pc2*) from Victoria blight susceptibility (*Vb*), neither conventional genetic (162, 239) nor mutagenic approaches, including the screening of millions of seedlings for naturally occurring mutants, have separated rust resistance from Victoria blight susceptibility (149, 150). Additional evidence that the *Pc2* gene and the *Vb* gene are either tightly linked or identical has come from an analysis of somaclonal variants generated under toxin selection in tissue culture (194). The results indicated that all plants regenerated from tissue culture lines that became victorin-insensitive also lost crown rust resistance. Thus, it appears that these genes are either very tightly linked or the same gene and, consequently, victorin may be interacting with a resistance gene to evoke responses that result in a susceptible interaction. Physiological studies of victorin support this connection, because victorin appears to induce many of the plant responses classically associated with avirulence elicitors, such as callose deposition (233), the respiratory burst (195), lipid peroxidation (176), ethylene evolution (205), extracellular alkalinization (226), phytoalexin synthesis (163), and K^+ efflux (242). Thus, genetic and physiological studies support the perception that victorin functions as an elicitor to induce components of a resistance response similar to those induced by avirulence factors. But why is victorin perceived as a toxin and assumed to induce host necrosis and facilitate pathogenesis by a necrotrophic fungus?

Evidence is accumulating that the HR cell death response often associated with induced resistance in gene-for-gene interactions is a type of programmed cell death (PCD) (53, 94, 102, 112, 133, 193). PCD is a genetically controlled, organized form of cellular suicide that normally functions to eliminate unnecessary or aged cells during morphogenesis (i.e., by cell selection) or cellular maturation. It is a "normal" form of cell death essential to cellular homeostasis in multicellular organisms. Thus, PCD is distinct from necrotic cell death, which typically arises as a result of severe cellular damage. Necrosis does not entail the participation

of the cell in its own destruction, as does PCD, but rather arises from a loss of function. The distinction between PCD and necrosis may be envisioned as the difference between "organized disassembly" and "death from damage."

Apoptosis, the most characterized form of PCD in animal systems, displays distinct morphological and biochemical characteristics. Morphologically, apoptosis is characterized by cell shrinkage, condensation of the chromatin, nuclear breakdown, membrane blebbing, and eventual fragmentation of the cell into apoptotic bodies. Visible changes in other organelles typically are minor (116, 230, 255). The biochemical markers of apoptosis include DNA fragmentation into nucleosomal fragments (254) (commonly referred to as DNA laddering), activation of a protease cascade involving unusual enzymes called caspases (67, 91, 103, 219) and, in most cases, mitochondrial dysfunction (2, 69, 103).

Victorin induces a form of PCD that shares many of the biochemical and morphological characteristics of apoptosis, including DNA laddering (176, 213, 258), heterochromatin condensation (258), cell shrinkage (99, 207; W. Bushnell, personal communication), and protease activation (176). Preliminary results indicate that protease activation occurs through a cascade involving the participation of caspase-like enzyme activities (W.C. Coffeen & T.J. Wolpert, unpublished). Furthermore, the signaling events leading to the host response to victorin also share characteristics with signaling events in resistance, including changes in calcium homeostasis and the participation of kinases and ethylene (104, 176, 213, 258). The similarity of the victorin-induced PCD response to the resistance-associated HR is directly reinforced by the observation that a similar response is induced in oats by incompatible isolates of *Puccinia coronata* and by treatment with nonspecific elicitors of the defense response (213). Those results are consistent with the finding that incompatibility of cowpea to the cowpea rust pathogen *Uromyces vignae* also shares some of the same characteristics (197), which are probably mediated by low-molecular-weight peptide elicitors (65).

Recent results have demonstrated that victorin contributes to mitochondrial dysfunction (52). This finding is noteworthy because, as mentioned above, mitochondrial dysfunction is commonly associated with the induction of PCD and because victorin had previously been shown to bind to members of the mitochondrial enzyme complex, glycine decarboxylase (GDC) (175, 251–253). In animal cells, the alteration in mitochondrial function associated with apoptosis is evidenced by a loss of mitochondrial transmembrane potential that is due to a mitochondrial permeability transition (MPT) possibly facilitated by the opening of the mitochondrial permeability transition pore (TP) (89, 93, 267). The MPT leads to an abrupt increase in permeability of the mitochondrial membranes to solutes with mol wt <1500 Daltons. When oat mitochondria in vitro undergo a MPT, victorin gains access to the mitochondrial matrix and binds to the GDC (52). Evidence is also consistent with the occurrence of a MPT in vivo during victorin-induced PCD (52). This and other observations have led to the speculation that, although binding of victorin to the GDC may contribute to mitochondrial dysfunction and consequently to PCD, the GDC is not the primary site of action for victorin. Rather,

the results suggest that victorin interacts with a site of action that is upstream of binding to the GDC (52). This initial site likely involves the product of the *Vb* gene, which remains unknown.

Thus, a variety of observations indicate that the response of oat to victorin shares many of the characteristics of an avirulence-elicited defense response. Whether victorin elicits these responses through a direct or indirect interaction with the product of a resistance gene remains to be determined. However, progress in this area may be forthcoming because victorin sensitivity has recently been identified in *A. thaliana*. This sensitivity, as in oat, appears to be conferred by a single dominant gene (J.M. Lorang, N. Carkachi-Salli & T.J. Wolpert, unpublished). This finding will facilitate a more direct evaluation of the possibility that victorin actually elicits a defense response. For example, identification of the gene conferring victorin sensitivity may provide insights into the function of the *Vb/Pc2* gene(s) in oats. It should also be possible to determine if mutations in any of the currently implicated defense pathways in *Arabidopsis* impact the effects of victorin.

AAL-Toxin

The AAL-toxins are a group of structurally related HSTs (22, 23, 30) produced by *Alternaria alternata* f. sp. *lycopersici* (82), with the most prevalent forms designated as AAL-toxin TA and TB. The pathogen causes Alternaria stem canker of tomato (95), and resistance to the disease and sensitivity to the toxin are conditioned by the *Asc* locus. Disease resistance is dominant, whereas toxin sensitivity is incompletely dominant. The homozygous recessive genotype is fully sensitive to the toxin, and the heterozygote displays intermediate sensitivity (46). Isolates incapable of producing AAL-toxins do not cause the disease (82), and mutants that are compromised in toxin production concomitantly lose their pathogenic phenotype (6).

The AAL-toxins induce an apoptotic-like response in toxin-sensitive tomato, as demonstrated by TUNEL-positive cells, DNA laddering, and the formation of apoptotic-like bodies (237). This PCD response, as in the HR, appears to involve calcium (237) and ethylene (83, 171) and, therefore, exhibits similarities to an induced resistance response. The AAL-toxins are part of a larger group of compounds structurally related to sphingosine and sphinganine, and are referred to as sphinganine analog mycotoxins, or SAMs. Other SAMs, known as fumonisins, are produced by the unrelated fungus *Fusarium verticillioides* (syn. *F. moniliforme*) and other *Fusarium* species (18). Interestingly, both fumonisin B1, the major fumonisin produced in culture, and AAL-toxin also induce apoptosis in monkey kidney cells (236). Fumonisin B1 (and other fumonisins) is as selectively toxic to the AAL-toxin sensitive tomato genotypes as the AAL-toxins (85, 135). This similarity in responses has led to the hypothesis that AAL-toxin–induced PCD likely involves ceramide signaling and disruption of the cell cycle (80, 81, 84). This speculation is supported by the fact that both fumonisin B1 and TA inhibit ceramide synthase in rat hepatocytes (170) and microsomal preparations from green tomato

fruit (83), with a concomitant alteration in the concentration of sphingoid bases (1). The recent cloning and characterization of the *Asc* locus in tomato also supports this hypothesis (26). The *Asc-1* gene is homologous to the yeast longevity assurance gene, *LAG1*, and has been proposed to compensate for depletion in ceramides by facilitating a sphingolipid-dependent transport mechanism either through the production of alternate ceramides or by encoding a SAM-insensitive sphinganine-*N*-acyltransferase (26). The recessive *asc-1* allele was found to contain a premature stop codon and, thus, likely encodes a nonfunctional truncated form of the protein (26).

Given the similarity in responses elicited by AAL-toxins and fumonisins, recent studies have provided particular relevance to a comparison of the responses evoked by HSTs and avirulence determinants (8, 211). Fumonisin B1 treatment of *A. thaliana* elicited a HR-like response that includes PCD, generation of ROS, deposition of phenolic compounds and callose, accumulation of phytoalexin, and expression of PR proteins (211). Further, this response requires jasmonate-, ethylene-, and salicylate-dependent signaling pathways (8) and, thus, appears remarkably similar to a defense response elicited by an avirulence determinant. Curiously, fumonisin B1-resistant *Arabidopsis* mutants were not noticeably compromised in their avirulence response to *avrRpt2*-expressing isolates of *Pseudomonas syringae* pv. *maculicola*, but these mutants did show enhanced resistance to virulent isolates of the pathogen (211).

T-Toxin

T-toxin, the HST produced by *Cochliobolus heterostrophus* (*Helminthosporium maydis* = *Bipolaris maydis*) race T and *Mycosphaerella zeae-maydis* (*Phyllosticta maydis*), is certainly the best-characterized HST in regard to its site and mode of action (141, 192). Both organisms produce a group of structurally related polyketides that are selectively toxic to maize (55, 124). Toxin-producing isolates are considerably more virulent than nonproducing isolates, and mutations in structural proteins required for toxin production clearly reduce virulence (261). *C. heterostrophus* causes Southern corn leaf blight, a disease of maize carrying Texas cytoplasm for male sterility (*cms-T*), and T-toxin is selectively toxic to *cms-T* maize. Parental lines with Texas male sterile cytoplasm were used extensively in hybrid seed production in the 1950s and 1960s because their use eliminated the need for hand emasculation. Consequently, most of the maize grown in the United States during this period was of this type (141, 192), which led to a major epidemic of the Southern corn leaf blight in 1970.

The association of toxin sensitivity with *cms-T* male sterility, a cytoplasmically inherited factor, led to the investigation of mitochondria as a possible site of action. These studies revealed that T-toxin selectively affected mitochondria isolated from *cms-T* plants compared to those that were isolated from normal cytoplasm (male fertile) maize. These responses include uncoupling of oxidative phosphorylation, stimulation of succinate- or NADH-driven state 4 respiration, inhibition of

malate-driven state-3 respiration, leakage of small molecules such as calcium and NAD^+, and mitochondrial swelling (141, 192). Analysis of the mitochondrial genome led to the discovery of a unique gene (T-*urf13*) in *cms-T* mitochondria, which apparently arose through recombination and encodes a protein of approximately 13 kDa (60). The *cms-T* genotype was also associated with a 13-kDa protein (URF13) that was localized to the mitochondrial membrane (62, 73, 74, 244). Definitive proof that URF13 conferred toxin sensitivity was achieved by expression of the T-*urf13* in *Escherichia coli*, which rendered these cells sensitive to T-toxin (61). The URF13 polypeptide associates predominantly as a tetramer in the mitochondrial membrane and, upon direct binding of T-toxin, undergoes a conformational change that leads to the formation of a pore in the mitochondrial membrane (141, 192). Pore formation leads to the observed effects on mitochondrial function through the leakage of cofactors, substrates and protons.

The pore-forming role of T-toxin is particularly compelling in the context of PCD. The mitochondrion, as discussed above, has been implicated as a key regulator of PCD in animals and recently has been proposed to play a similar role in PCD in plants (111, 133). In animals, the apoptotic response is often associated with permeabilization of the mitochondrial membrane through induction of pore formation. A number of pro-apoptotic proteins, such as Bax, have been proposed to lead to pore formation either indirectly through interaction with an endogenous pore-forming mechanism (the TP, discussed above) or directly by forming a pore in mitochondrial membranes (2, 51, 103, 159). Further, expression of Bax in tobacco leads to a response with phenotypic similarities to the HR, including the induced expression of PR proteins (132). Given that T-toxin induces a pore through interaction with URF13, it is possible that T-toxin produces responses similar to the expression of Bax. This speculation gains credibility with the recent association of cytoplasmic male sterility and PCD (14). It will be important to evaluate the cell death phenotype induced by T-toxin in the context of PCD and other responses associated with the resistance response. Does T-toxin induce DNA laddering, an oxidative burst, and the accumulation of PR proteins? Studies of this nature could provide a unique opportunity to investigate mechanistic links between the regulation of PCD in plants and animals and evaluate the association of PCD with resistance and susceptibility.

HC-Toxin

Cochliobolus carbonum (*Helminthosporium carbonum* = *Bipolaris zeicola*) causes Northern leaf spot and ear rot of maize. Of the three races of the pathogen that have been reported, only race 1 produces HC-toxin, a cyclic tetrapeptide with host-selective activity against susceptible genotypes of maize (96, 143, 189, 201, 234). The non-toxin–producing races (race 2 and race 3) are common and prevalent throughout the world but cause smaller lesions and less damage on a diverse range of maize genotypes than the combination of race 1 on toxin-sensitive maize (201, 228, 229). Thus, HC-toxin is considered a virulence factor, because race 1

exhibits increased lesion size on sensitive maize, but the toxin is not required for pathogenicity of the species.

Resistance to *C. carbonum* race 1 and insensitivity to HC-toxin are determined by the dominant allele at the *Hm1* locus (177, 227). The *Hm1* gene encodes a carbonyl reductase, HC-toxin reductase (HCTR) (107), which inactivates the toxin by enzymatically reducing the ketone function (168, 169) on the side chain of the 2-amino-8-oxo-9,10-epoxyoctadecanoic acid (aoe) residue, which in addition to the epoxide moiety of aoe (42, 232) is essential for toxic activity (117). Genotypes homozygous for transposon-disrupted *Hm1* (107, 168) or naturally occurring mutants with disrupted *Hm1* (172) (commonly designated *hm1 hm1*) lack the HCTR activity and are fully susceptible to *C. carbonum* race 1.

Some effects of HC-toxin on host plant tissues could be construed as beneficial. Many of these effects are directly opposed to those induced by other HSTs. Instead of inducing a general leakage of electrolytes, HC-toxin increases uptake of organic and inorganic solutes by susceptible maize roots (264) and stimulates uptake, accumulation, and reduction of nitrate (263). In contrast to the effects of most HSTs on cell membranes, HC-toxin induces membrane hyperpolarization of susceptible maize cells rather than depolarization (79). Further, instead of killing protoplasts, HC-toxin increases the long-term viability of leaf protoplasts a few days beyond that of protoplasts incubated in the absence of HC-toxin (245). Most of the effects of HC-toxin also are observed with tissues of the resistant genotype but only at toxin concentrations 100- to 200-fold higher than those that affect the susceptible genotype.

Also in contrast to the HSTs described above, there is no evidence to suggest that HC-toxin elicits defense responses (ROS, PCD, phytoalexin accumulation, alterations in membrane permeability, etc.) in the toxin-sensitive host. Available evidence, in fact, indicates that HC-toxin prevents the operation of resistance mechanisms and functions as a suppressor of defense responses (34, 66). Inoculation of leaves of the susceptible genotype with conidia of the non-toxin–producing race 2 in combination with HC-toxin or following prior treatment with toxin, results in the expression of full susceptibility to the otherwise weakly virulent pathogen (32, 49), suggesting that host responses that restrict the ability of race 2 to infect are compromised by HC-toxin. More significantly, in converse experiments, prior inoculation of toxin-sensitive maize leaves with conidia of race 2, a non-toxin–producing race, induces localized resistance that is effective against race 1, the toxin producer. Prior inoculation with race 2 reduces the expression of disease symptoms elicited by race 1 to those indistinguishable from symptoms elicited by race 2 (32, 33). However, application of HC-toxin abolishes the induced resistance, again suggesting a role of HC-toxin in preventing the host from mounting an effective defense.

Among the genotype-specific responses elicited by HC-toxin is an alteration in protein synthesis, resulting in the expression of a few new proteins and the suppressed synthesis of others when compared to proteins synthesized by the resistant genotype and by both genotypes treated with inactivated toxin (41). These

proteins have not been identified, and no cause-and-effect relationship with the disease phenotype has been documented. However, HC-toxin has no effect on amino acid incorporation (41, 264) or on in vitro translation of maize mRNA (41), indicating that the toxin does not inhibit processes directly involved in protein synthesis. Thus, it is tenable to propose that HC-toxin influences gene expression, which impacts the expression of defense (13, 231). HC-toxin, as well as structurally related cyclic tetrapeptides, inhibits histone deacetylase (HDAC) from a variety of organisms (27). Treatment of maize embryos and tissues cultures with HC-toxin and infection of susceptible but not resistant leaves results in the accumulation of hyperacetylated forms of core histones (191). However, Baidyaroy et al. (10) discount the role of HC-toxin as a suppressor of defense responses and argue that, because HDACs can function as corepressors, the maize defense genes may be overexpressed during infection. Thus, although HDACs likely are primary sites of HC-toxin action (191), the issue of the consequences of effects on gene expression remains unresolved.

Examination of the mode of action of HC-toxin clearly indicates that it does not induce responses similar to the host defense response. Consequently, it shows no similarity to avirulence elicitors in this regard. However, the results do show that, ironically, HC-toxin has little toxicity yet clearly functions as a virulence factor. Also, it appears likely that it affects gene expression and can interfere with expression of the defense response. These activities of HC-toxin are remarkably similar to a proposed role of avirulence determinants in virulence. Some avirulence proteins may function like the virulence factors of *Yersinia* sp. (and related bacteria) to interfere with the signaling and structural pathways of host defense (208, 243). Thus, HC-toxin may share functional similarities with avirulence factors. Perhaps establishing the mode of action of HC-toxin will contribute to an understanding of the role of avirulence factors in conferring virulence in the absence of their corresponding resistance gene.

Other HSTs

The precise mode of action of most of the HSTs remains unknown. However, available evidence from a number of examples suggests that HST activity requires an active host response. The active participation of the host in its own cell death is inconsistent with a necrotic response and is suggestive of a form of PCD. Toxins other than the ones discussed above appear to involve such active host responses. For example, the toxic effects of peritoxin (PC-toxin), the HST produced by the soilborne pathogen of sorghum, *Periconia circinata* (154), are inhibited by cycloheximide and cordycepin, inhibitors of protein and RNA synthesis, respectively (247). PC-toxin treatment of toxin-sensitive sorghum also induces the increased synthesis of a number of proteins (247), a response reminiscent of the induction of PR proteins in the defense response. Interestingly, one of the earliest ultrastructural changes induced in the host by PC-toxin is highly condensed heterochromatin (7), one of the hallmarks of apoptosis. Also, cycloheximide has been demonstrated

to inhibit the toxic effects of AK-toxin, the HST produced by the pathotype of *Alternaria alternata* that causes black spot disease of Japanese pear (122). This toxin also induces the active synthesis of callose (182, 185), a response indicative of the resistance response. Some effects of Ptr ToxA, one of the protein HSTs produced by *Pyrenophora tritici-repentis*, causal agent of tan spot of wheat, are also influenced by temperature and inhibitors of RNA and protein synthesis, with the latter preventing the onset of necrosis (43, 130, 131).

CELL DEATH, COMPATIBILITY, AND INCOMPATIBILITY

A necrotroph is a pathogen that kills host tissue as it colonizes and obtains nutrients from the killed cells (210). Most toxin-producing pathogens, including those that produce HSTs, are considered necrotrophs. At least some HSTs elicit a response that requires the participation of the host in regulating cell death. This observation not only begs the question of whether these compounds should be called toxins, but also indicates that the pathogen per se does not kill the host but that the host "kills itself." Further, the association of markers typical of the resistance response with those of cell death suggests that, in some cases, the pathogen may be taking advantage of resistance responses to facilitate pathogenesis. This mechanism of involving the participation of the host in its own cell death may not be unique to the HST-producing fungi discussed above. For example, it has been demonstrated that the expression of a number of antiapoptotic genes, including the human *Bcl-2* and *Bcl-xl* genes, the nematode (*Caenorhabditis elegans*) *CED-9* gene, and the baculovirus *Op-IAP* gene, can impact pathogenesis by a number of necrotrophs (64). Transgenic plants expressing these genes were resistant to the necrotrophs *Sclerotinia sclerotiorum*, *Botrytis cinerea*, and the toxin-producing necrotroph, *Cercospora nicotianae*. This resistance appeared to be dependent on the prevention of PCD. Inoculation of wild-type plants with *S. sclerotiorum* resulted in a susceptible response and was associated with the formation of DNA ladders, typical of a PCD response. PCD was prevented in transgenic plants expressing *Bcl-2*-mediated resistance. Also, transgenic plants expressing a mutant of *Bcl-xl*, which compromises its antiapoptotic function in animals, also failed to confer resistance to *S. sclerotiorum*. This suggests that successful colonization of the host by those pathogens is dependent on active host participation at least through regulation of PCD.

The dependence of *S. sclerotiorum*, *B. cinerea*, and *C. nicotianae* on host PCD for pathogenesis is particularly significant given that the generation of ROS has been implicated as essential for pathogenesis in each of those pathogens. Thus, events commonly associated with resistance, an HR-like PCD response and ROS formation, are involved in susceptibility. ROS generation and concomitant redox signaling have been proposed to play a central role in the integration of the diverse array of plant defense responses (53, 92, 98, 257), and the production of ROS, irrespective of the source or even the chemical nature of the ROS, may be sufficient

to elicit the defense response (198). Accordingly, the generation of ROS suggests that the defense response is activated. Cercosporin, the toxin produced by many *Cercospora* species, when activated by light in the presence of oxygen, elicits the production of singlet oxygen and superoxide (56, 57). Also, *S. sclerotiorum* (90) and *B. cinerea* (59, 90, 220) induce ROS production by the host. The extent of ROS generation induced by *B. cinerea* is positively correlated with the ability of a given isolate to cause disease (59, 220), and enhanced ROS production in the host is correlated with increased virulence of *B. cinerea* and *S. sclerotiorum*. Conversely, inhibition of ROS formation with diphenyleneiodonium, a putative inhibitor of the NADPH-dependent oxidase system, compromises susceptibility (90). Susceptibility also was compromised in the HR-deficient *dnd1* mutant of *Arabidopsis*, and the resistance response elicited by an avirulent race of *Pseudomonas syringae* enhanced susceptibility to *B. cinerea* (90). These results support the contention that these organisms exploit the host resistance response for susceptibility. The association of susceptibility with the induction of ROS also is indicated by the interaction of *Drechslera* species with oats (87) and *Bipolaris sorokiniana* with barley (129).

A biotroph is a pathogen that obtains organic nutrition from living cells of the host (210), and a hemibiotroph exhibits both necrotrophic and biotrophic phases during disease development (108). Microorganisms that produce avirulence determinants can display necrotrophic, biotrophic, and hemibiotrophic lifestyles. Host cell death in the form of the HR commonly associated with the resistance response has been suggested (98, 101, 102), with some supportive data (202), to be an important component of the defense response for obligate biotrophs. However, a general role for host cell death in resistance (as with other resistance-associated responses), particularly in necrotrophs and hemibiotrophs, is not obvious (193). In some cases, cell death does not appear to contribute substantially to the resistance response (265).

HST-producing fungi are considered to be necrotrophs, and a role of host cell death in susceptibility is generally accepted. However, even in these examples, a role for cell death in susceptibility is not always apparent. HC-toxin clearly facilitates pathogenesis but, as summarized above, is thought to be cytostatic rather than toxic (231). Thus, host cell death does not seem to be a consistent requirement for pathogenesis. Careful examination of growth of *C. victoriae* in susceptible and resistant oats also suggests that cell death may not be necessary for pathogenesis (262). In these experiments, conidia of *C. victoriae* attached, germinated, formed appressoria, and penetrated the leaf surface. Both toxin-producing and nonproducing isolates developed to the same extent up to about 8–12 h after inoculation. After this time, toxin-producing (pathogenic) isolates produced intercellular and intracellular hyphae, which continued to ramify through the tissue of susceptible oats. By 24 h, the mesophyll contained numerous hyphae, and by 48 h, leaf tissue was overrun by the fungus. However, the first visible effects on the host cells were noted at about 48 h. Separation of host cell death and pathogenesis has also been indicated in the interactions of AK-toxin-producing isolates of *A. alternata* that are

pathogenic on Japanese pear and AM-toxin-producing isolates that are pathogenic on apple (122). Pretreatment of the toxin-sensitive pear with agents that prevent AK-toxin-induced necrosis did not affect disease development. Also, it was found that light suppressed AM-toxin–induced host necrosis but had no effect on the rate of fungal infection of toxin-sensitive apple leaves by toxin-producing isolates.

It would also appear that, in at least some cases, host cell death is not sufficient for pathogenesis by HST-producing organisms. For example, some *Fusarium* species produce SAMs that produce the same effects as AAL-toxins (above) and yet are not pathogenic on tomatoes. A recent study by Brandwagt et al. (25) identified a number of *Nicotiana* species that are sensitive to AAL-toxins, yet the majority of those species were resistant to infection by *A. alternata* f.sp. *lycopersici*. *Cochliobolus* species are noted for their production of HSTs, and these fungi commonly infect grasses. However, preliminary results indicate that transformation of *C. carbonum* with the *ToxA* gene, which confers pathogenicity to nonpathogenic isolates of *Pyrenophora tritici-repentis* (45), the causal agent of tan spot of wheat, does not enable the Ptr ToxA-producing transformants to be pathogenic on wheat (L.M. Ciuffetti, unpublished). The recent discovery of victorin-sensitive *Arabidopsis* genotypes should provide an opportunity to determine whether sensitivity to victorin is sufficient to promote pathogenesis by toxin-producing isolates of *C. victoriae*.

Thus, just as the role of host cell death in resistance in gene-for-gene interactions is ambiguous, the same may be true for its role in susceptibility to many HST-producing fungi. While host cell death may contribute to resistance in some gene-for-gene interactions, it may be neither necessary nor sufficient for resistance in others. In diseases caused by some HST-producing fungi, host cell death is likely to play a role in susceptibility. However, the role of host cell death in susceptibility to all HST-producing fungi is not clear, nor is it clear that all HST-producing fungi are strictly necrotrophs, deriving nutrients only from killed cells with cell death sufficient for pathogenesis.

STRUCTURE AND BIOSYNTHESIS

Some of the HSTs that have been chemically characterized are listed in Table 1. Most HSTs are low-molecular-weight, diverse secondary metabolites that exist as families of structurally similar compounds. As a group, HSTs affect a range of monocotyledonous and dicotyledonous plants (Table 1). The following examples of some selected HSTs illustrate the diversity of structures and mechanisms of biosynthesis.

Alternaria alternata

The various pathotypes of *Alternaria alternata* are determined by the toxins they produce and, consequently, the hosts that are sensitive to their HSTs. The HSTs produced by a particular pathotype of *A. alternata* are usually multiple forms of related

TABLE 1 Examples of host-selective toxins

Pathogen	Host/Pathotype	Toxin	Chemical class[a]	Sus/Sen[b]
Alternaria alternata	Japanese pear	AK-toxin	Epoxy-decatrienoic esters	Dominant
	Strawberry	AF-toxin	Epoxy-decatrienoic esters	Dominant
	Tangerine	ACT-toxin	Epoxy-decatrienoic esters	Dominant
	Apple	AM-toxin	Cyclic tetrapeptide	Dominant
	Tomato	AAL-toxin	Aminopentol esters	Recessive[c]
	Rough lemon	ACR(L)-toxin	Terpenoid	Dominant
Bipolaris sacchari	Sugarcane	HS-toxin	Glycosylated sesquiterpene	—
Cochliobolus carbonum	Corn	HC-toxin	Cyclic tetrapeptide	Recessive
Cochliobolus heterostrophus	Corn	T-toxin	Linear polyketols	Cytoplasmically inherited
Cochliobolus victoriae	Oats	Victorin	Cyclized chlorinated peptide	Dominant
Mycosphaerella zeae-maydis	Corn	PM-toxin	Linear polyketols	Cytoplasmically inherited
Periconia circinata	Sorghum	Peritoxin	Peptidyl chlorinated polyketide	Incompletely dominant
Pyrenophora tritici-repentis	Wheat	Ptr ToxA	13.2-kDa protein	Dominant
	Wheat	Ptr ToxB	6.6-kDa protein	Dominant

[a]Chemical class descriptions for the HSTs produced by *Alternaria alternata* were taken from Brandwagt (24).

[b]Susceptibility to the fungus and sensitivity to the toxin.

[c]Susceptibility to the fungus is recessive and sensitivity to the toxin is semidominant.

compounds (123, 179, 182, 231). The HST-producing species of *Alternaria* are intriguing examples of intraspecific variation and of the evolution of pathogenicity governed by specific phytotoxic metabolites (216). For example, AK-toxins are produced by the Japanese pear pathotype (causal agent of black spot of Japanese pear), ACT-toxins are produced by the tangerine pathotype (causal agent of brown spot of tangerine), and AF-toxins are produced by the strawberry pathotype (causal agent of Alternaria black spot of strawberry) (174). All of those HSTs have a common moiety, 9,10-epoxy-8-hydroxy-9-methyl-decatrienoic acid, that serves as a precursor to the toxins (68, 174, 216). REMI (restriction enzyme-mediated integration) was used to mutagenize and tag the *AKT1* and *AKT* genes, which are required for AK-toxin biosynthesis and pathogenicity of the Japanese pear pathotype (216). Homologues of *AKT1* and *AKT2* are present also in isolates of the tangerine and strawberry pathotypes (161, 216). In further studies, the complex genomic region that controls AK-toxin biosynthesis was shown to contain two additional genes,

AKT3 and *AKTR*, also necessary for AK-toxin production. *AKT1*, *AKT2*, *AKT3*, and *AKTR* and their homologues are present on a single chromosome (217).

AM-toxin, produced by the apple pathotype of *A. alternata* (causal agent of *Alternaria* blotch) is a four-membered cyclic depsipeptide (180, 225). Recently, a 13.1-kb cyclic peptide synthetase gene, *AMT*, was cloned and found to be absent from non-toxin-producing isolates of *A. alternata* (110). Disruption of *AMT* or spontaneous loss of the 1.1-Mb conditionally dispensable chromosome resulted in mutants that are unable to produce AM-toxin and are no longer pathogenic (109).

AAL-toxins, produced by the tomato pathotype of *A. alternata* (causal agent of *Alternaria* stem canker of tomato), as mentioned above, are structurally related to fumonisins and, thus, are members of the sphinganine analog mycotoxins (SAMs) (18, 30, 82, 83, 236). Not surprisingly, *A. alternata* f.sp. *lycopersici* also produces fumonisin B_1 (36). AAL-toxins consist of an aminopentol backbone that is esterified to a tricarboxylic acid group, and each analogue has two isomers (22–24). AAL-toxin-deficient REMI mutants are nonpathogenic on tomato and characterization of these mutants is in progress (6).

Bipolaris sacchari

HS-toxins (HS-toxin A, B, and C) produced by *Bipolaris* (*Helminthosporium*) *sacchari*, the causal agent of eyespot disease of sugarcane, are composed of four galactose units linked to a sesquiterpene aglycone ($C_{15}H_{24}O_{22}$), which can occur in three isomeric forms in toxins designated $A_{2,2}$, $B_{2,2}$, or $C_{2,2}$ (147, 151–153, 261). The aglycone C was isolated from the mycelium of the fungus and proposed to be a biosynthetic precursor based on incorporation of exogenously supplied ^{3}H-aglycone into active HS-toxin by *B. sacchari* cultures (173). The appearance of inactive HS-toxin analogs with 1, 2, or 3 galactose units linked to the sesquiterpene in culture filtrates of *B. sacchari* (147) was found to be associated with degradation of the active toxin resulting from an increase in activity of β-galactofuranosidase (146).

Cochliobolus Species

HC-toxin is a family of cyclic tetrapeptides, with *cyclo*-(D-proline-L-alanine-D-alanine-L-2-amino-8-oxo-9,10-epoxydecanoic acid) as the predominant form (96, 189, 234) produced by race 1 isolates of *Cochliobolus carbonum*. HC-toxin production is controlled by a single Mendelian locus, *Tox2*, a complex locus composed of multiple copies of multiple genes. HC-toxin is produced by a 570-kDa non-ribosomal peptide synthetase, called HC-toxin synthetase (HTS), encoded by *HST1* (184, 204). Two functional copies of *HST1* are found only in race 1 isolates of *C. carbonum*. In addition to *HST1*, other genes of *Tox2* have been identified and characterized. *TOXA* encodes an HC-toxin efflux pump (188); *TOXC* encodes a beta subunit of fatty acid synthase (4); *TOXF* encodes a putative branched-chain amino acid aminotransferase (37); *TOXG* encodes an alanine racemase that functions in the synthesis of D-Ala (38); and *TOXE* likely encodes a regulatory protein,

but is not required for the expression of *HST1* (5). The multiple genes in *Tox2*, with the exception of one copy of *TOXE*, are physically linked within an approximately 600-kb region (2a, 38). *Tox2* is present on different chromosomes in different groups of race 1 isolates (3, 31).

T-toxin (HMT-toxin or BMT-toxin) is a mixture of linear polyketols (C_{35} to C_{41}) produced by race T isolates of *Cochliobolus heterostrophus*, causal agent of Southern corn leaf blight (124, 128, 186). The major difference between race T isolates and the less virulent race O isolates of *C. heterostrophus* is the *Tox1* locus (138) and the production of T-toxin. *Tox1* is associated with the breakpoints of a reciprocal translocation (35, 224). Based on genetic and physical analyses, *Tox1* is comprised of two unlinked loci, *Tox1A* and *Tox1B*, which are on different chromosomes (118). Tagged mutations at *Tox1* led to the cloning of *PKS1*, which encodes a polyketide synthase (148, 256), and *DEC1*, which has similarity to decarboxylases (196). Targeted inactivation of either of these genes results in the loss of T-toxin production and, thus, virulence on T-cytoplasm corn (118, 196, 256).

Mycosphaerella zeae-maydis (*Phyllosticta maydis*), causal agent of yellow leaf blight of corn, produces a HST, PM-toxin (48, 259). PM-toxin is a family of long-chain linear polyketols (C_{33} and C_{35}) that are structurally similar to T-toxin (55, 125). As with T-toxin, PM-toxin is selectively active against T-cytoplasm corn and specifically binds to the T-urf13 protein (62, 75). Because of the similarities in structure, specificity, and site and mode of action of PM-toxin and T-toxin, the biosynthesis of these toxins may be similar in *M. zeae-maydis* and *C. heterostrophus*.

Victorin, the HST produced by *Cochliobolus victoriae*, is composed of a group of closely related cyclized pentapeptides. The predominant form of the toxin in culture, designated victorin C, is composed of glyoxylic acid and a cyclic combination of five unusual amino acids: 5,5-dichloroleucine, threo-β-hydroxylysine, erythro-β-hydroxyleucine, α-amino-β-chloro-acrylic acid, and 2-alanyl-3,5-dihydroxycyclopentenone (victalanine) (155, 250). A number of other naturally occurring structural variants of victorin have been characterized and given the trivial names of victorin B, D, E, and victoricine (249). Those forms of victorin differ from victorin C in the extent of the chlorination of the N-terminal leucine residue (victorins B and E), in the absence of a hydroxyl group on the victalanine residue (victorin D), or a complete lack of chlorination at the leucine residue and the replacement of victalanine with 2,5 DOPA (victoricine). Another form of victorin, designated HV-toxin M, was identified and characterized by Kono et al. (127). This form of the toxin is identical to victorin C except that it contains a glycine residue instead of the glyoxylic acid. Only minor differences in activities of the various forms of victorin are observed (248) with the exception of HV-toxin M, which appears to exhibit substantially lower activity than the other forms (127).

The molecular genetics of victorin biosynthesis is being investigated. A REMI mutant of *C. victoriae* has been identified that lacks victorin production and is no longer pathogenic (261; A.C.L. Churchill, W. Lu, O.C. Yoder, B.G. Turgeon &

V. Macko, unpublished). It is anticipated that a peptide synthetase is involved in victorin biosynthesis.

Periconia circinata

Periconia circinata, causal agent of sorghum root rot, produces a group of low-molecular-weight HSTs called peritoxins (PC-toxin) (39, 154, 190, 246). Peritoxins A and B are selectively toxic and consist of a cyclized peptide and a chlorinated polyketide (39, 154). Inactive intermediates have been identified and characterized and these, along with peritoxins A and B, are absent from nonpathogenic, non-toxin-producing strains of *P. circinata*. Based on those studies, it was proposed that a peptide synthetase and a polyketide synthase are involved in the biosynthesis of peritoxins (39).

Pyrenophora tritici-repentis

In contrast to other HST toxins, the HSTs thus far characterized from *Pyrenophora tritici-repentis* (causal agent of tan spot of wheat) are ribosomally synthesized proteins. Ptr ToxA (syn. Ptr necrosis toxin, Ptr toxin, ToxA) is a 13.2-kDa protein and Ptr ToxB (syn. Ptr chlorosis toxin) is a 6.6-kDa protein (15, 40, 212, 222, 223, 266). Other host-selective activities, in addition to Ptr ToxA and Ptr ToxB, have been identified, but these putative HSTs have not been characterized (28, 43, 63, 223). Recently, Effertz et al. (67a) partially purified a third host-selective toxin produced by *P. tritici-repentis* and designated this toxin, Ptr ToxC (syn. Ptr chlorosis toxin). Based on the characterization thus far, Ptr ToxC appears to be a polar, nonionic, low-molecular-weight molecule (67a). Based on the ability of an isolate to induce necrosis and/or chlorosis on a set of wheat differentials, a race designation system was proposed by Lamari et al. (134) that distinguishes 5 races. The development of these symptoms was found to be dependent upon a specific combination of the host genotype and the isolate of *P. tritici-repentis* tested. It is likely that, in this disease interaction, race specificity is dictated primarily by the production of a combination of multiple HSTs.

Two groups independently cloned a cDNA for the major necrosis-inducing toxin, Ptr ToxA (16, 44, 45). Sequence analysis of the cDNA clone indicated that *ToxA* (syn. *PtrNEC*) encodes a 19.7-kDa preproprotein. The precursor is composed of a signal peptide necessary for secretion, a small domain at the N terminus comprising an anionic peptide that is not present in the mature toxin, and a larger domain at the C terminus comprising the mature, cationic toxin. A genomic clone of the *ToxA* gene was isolated along with its endogenous promoter, and expression was shown to be sufficient for pathogenicity. When transformed into a non-toxin-producing, nonpathogenic isolate of the fungus, the *ToxA* gene conferred upon this isolate toxin-producing ability and pathogenicity (45). In isolates analyzed thus far, the *ToxA* gene appears to be a single-copy gene that is absent from non-toxin-producing isolates of *P. tritici-repentis* (16, 44, 45). Recently, the *ToxB* gene was cloned and characterized from a race 5 isolate of *P. tritici-repentis* (158). In

contrast to Ptr ToxA, Ptr ToxB is a single-domain protein. The *ToxB* gene contains a 261-bp open reading frame that encodes a 23-amino acid signal peptide and a 64-amino acid HST. In contrast to *ToxA*, at least five copies of the *ToxB* gene are present in race 5 isolates tested (158). Interestingly, nonpathogenic isolates of *P. tritici-repentis* contain a single-copy gene (*toxb*) with 86 % identity to *ToxB* at the nucleotide level (J.P. Martinez & L.M. Ciuffetti, unpublished).

In addition to the protein toxins of *P. tritici-repentis*, Otani et al. (183) reported the isolation of a 35-kDa HST (AB-toxin) from *Alternaria brassicicola*, causal agent of black leaf spot. This proteinaceous HST awaits further characterization and stands in contrast to other HSTs produced by *Alternaria* species.

Other HSTs

Additional HSTs or potential HSTs have been documented in the literature. Examples include: maculosin from *A. alternata* on spotted knapweed (20, 209), ACRL-toxin from *A. alternata* on rough lemon (78, 121, 182), AT-toxin from *A. alternata* on tobacco (119, 120), ACTG-toxin from *A. alternata* on tangerine (126), AS-I toxin from *A. alternata* on sunflower (142), SV-toxins from *Stemphylium vesicarium* on European pear (206), and destruxin B from *A. brassicae* on brassicas (9, 11, 29, 187, 238).

Avirulence Gene Products

A comparison of the structures of most HSTs with avirulence gene products would suggest few similarities. However, clear exceptions to this are the protein HSTs produced by *P. tritici-repentis*, the causal agent of tan spot of wheat. In this interaction, the differential production of toxins dictates a complex race structure. Further, two of the toxins have been characterized and shown to be proteins, direct gene products, and single dominant genes in the host confer sensitivity to each of these toxins. These features bear similarities to most of the avirulence determinants characterized from fungi, particularly those from the tomato pathogen *Cladosporium fulvum*. Because of the genetic pattern of toxin production and host sensitivity, tan spot of wheat appears to be a true gene-for-gene interaction except that virulence and compatibility, rather than avirulence and incompatibility, are the dominant features.

Most of the remaining HSTs that have been characterized appear to be the products of multifunctional enzymes or enzymatic pathways and exist as families of compounds. Consequently, they are considered secondary metabolites. This appears in marked contrast to the majority of avirulence determinants, which appear to be proteins. However, obvious exceptions to this are the syringolide avirulence elicitors. The syringolides are a group of glycolipid secondary metabolites produced as a consequence of the expression of allelic variants of *avrD* and are comprised of three closely related structures. Syringolides 1 and 2 are produced by class I alleles of *avrD*, and syringolides 1 and 3 are produced by class II

alleles (106). Hence, syringolides are exceptional because they are secondary metabolites that serve as avirulence elicitors. However, it is important to realize that most of the avirulence determinants have been characterized only genetically. The role of these determinants in virulence and/or avirulence is not understood, and they typically show little homology to other proteins in existing databases (208). Consequently, in most cases, it has not been established that the protein product of the given avirulence gene directly serves as the elicitor. Clues that this may not always be the case come from *AvrBs2*, which appears to encode an enzyme with similarities to agrocinopine synthase and glycerol phosphodiesterase (243), the YopJ family of avirulence determinants, which may be cysteine proteases (208), and *Avr-Pita*, which encodes a zinc metalloprotease (105). Thus, while most HSTs appear to be secondary metabolites and most avirulence determinants may be proteins, reciprocal examples of both exist. Consequently, an examination of structures serves little to differentiate their functions in determining the outcome of a disease interaction.

CONCLUDING REMARKS

In this article, we have compared host responses to HSTs, "agents of compatibility," and avirulence determinants, "agents of incompatibility." These comparisons are admittedly tenuous given the general lack of understanding about the function and mode-of-action of these determinants. However, in some cases, it would appear that significant characteristics are shared by each and that evidence can be found that some HSTs elicit an active host response that is remarkably similar to the resistance response elicited by avirulence determinants. Also, in some cases, HSTs may function to confer virulence in a manner similar to the proposed role in virulence for some avirulence determinants in the absence of their cognate resistance gene. This suggests that a deeper understanding of each of these determinants could be mutually beneficial and contribute substantially to our understanding of the development of the disease process.

The suggestion that HSTs, in some cases, may be evoking defense responses may not be surprising given that many defense responses are often elicited in the later stages of compatible interactions and differences in the intensity and timing of such responses may be the factors that determine the outcome of the disease interaction. In the absence of thorough comparative studies, or definitive evaluation of the mode-of-action of the HSTs implicated, this possibility cannot be discounted. However, if it is accepted that some HSTs function by directly eliciting the defense response, a number of interesting theoretical and practical questions arise. Do any of the responses commonly associated with defense actually confer resistance or are some of these HST-producing fungi "immune" to the defense response? If some of these fungi are unaffected by the defense response, did this require coevolution with the host? Alternatively, could sensitivity toward host defense be an evolved response?

Also, if resistance-associated host cell death is sufficient for pathogenesis by necrotrophs that produce HSTs, why is it not sufficient for necrotrophs that produce avirulence determinants? Finally, if some organisms can exploit the defense response for pathogenesis, then is it possible that engineering plants to initiate this response when confronted by any invading microorganism could, in some cases, result in disease development?

A comparison of plant responses to HSTs and avirulence determinants indicates that there are no host responses that are clearly definitive markers of disease resistance or susceptibility and that the role of the pathogen is as important as the host defense response in determining the outcome of the disease interaction. Defining how HSTs contribute to compatibility will further our understanding of plant host/pathogen interactions.

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