The Role of Fungal Secondary Metabolites and sRNAs

Subjects: Agronomy

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Fungal plant pathogens use proteinaceous effectors as well as newly identified secondary metabolites (SMs) and small non-coding RNA (sRNA) effectors to manipulate the host plant's defense system via diverse plant cell compartments, distinct organelles, and many host genes. However, most molecular studies of plant–fungal interactions have focused on secreted effector proteins without exploring the possibly equivalent functions performed by fungal (SMs) and sRNAs, which are collectively known as "non-proteinaceous effectors". Fungal SMs have been shown to be generated throughout the plant colonization process, particularly in the early biotrophic stages of infection. The fungal repertoire of non-proteinaceous effectors has been broadened by the discovery of fungal sRNAs that specifically target plant genes involved in resistance and defense responses. Many RNAs, particularly sRNAs involved in gene silencing, have been shown to transmit bidirectionally between fungal pathogens and their hosts.

SMs sRNAs interactions

1. Introduction

Plants have developed a broad spectrum of responses to counter pathogen invasion. Likewise, plant pathogens orchestrate a highly calibrated array of pathogenicity strategies in their quest to cause diseases [1]. The recent increased availability of fungal and plant genomes in the public domain has facilitated considerable progress in molecular plant–fungal interaction studies. During interaction with their hosts, fungal plant pathogens secrete many proteins known as effectors which manipulate the physiology of the host or suppress the host's immunity to promote infection [2][3]. Most studies on effectors have focused almost exclusively on secreted proteins, without exploring the possibly equivalent functions performed by fungal secondary metabolites (SMs) (chemical effectors) and sRNAs (sRNA effectors) which are collectively referred to as non-proteinaceous effectors [2][4]. Accumulating evidence has indicated that, pathogens use sRNAs (such as siRNAs and microRNAs) and SMs to manipulate host cell functions [5][6]. Fungal SMs and sRNAs have been shown to manipulate host defense-related genes in the same was as proteinaceous effectors [7][8]. In general, SM and sRNA effectors are increasingly becoming important targets for studying the pathogenesis mechanisms of fungal pathogens [9].

2. Fungal Secondary Metabolites Enhance Pathogenicity during Plant-Fungal Pathogen Interactions

Fungal SMs are not required for the growth and development of the fungus, but they have the potential to improve the pathogen's fitness under certain conditions. Fungal SMs are often divided into polyketides, terpenes, non-ribosomal peptides and alkaloids on the basis of the primary enzymes and precursors that are involved in their biosynthesis [10][11]. The existence of fungal SMs, which have no discernible effect on the viability of the producer, raises issues about their potential influence on the environment [12]. SMs production by fungal pathogens and the presence of a host protein that is specifically susceptible to the corresponding toxin determines the ability of the pathogen to infect the host plant. Because host-specific toxin targets are encoded by plant genes, such genes can be referred to as dominant susceptibility genes [13]. Accumulating evidence indicates that fungal SMs serve as avirulence factors, host defense suppressors, and fungal cell wall hardening factors [8][14]. Fungal SMs are most effective during the early stage of infection (biotrophic phase), enhancing the fungus' ability to penetrate and colonize its host without killing its host [2]. Fungal SMs can be host specific or non-host specific and generate necrosis in plant tissue. The majority of the fungal SMs have not been defined chemically, and the plants that they are intended to affect are still a mystery. The biological actions that have been reported to be caused by fungal SMs generated in-planta suggest that they have a broad range of plant cellular targets. The production and transport of proteins are targets of a wide range of fungal SMs [15][16].

3. Small non-coding RNAs—The Secret agents in Plant-Fungal Pathogen Interactions

Plant immune responses are tightly regulated by an array of immunity-associated regulators such as sRNAs and some transcription factors [17]. Based on their biogenesis and structural features, sRNAs can be classified into three categories: short-interfering RNAs (siRNAs), dicer-independent microRNAs (miRNAs) and dicer-independent piwi interacting RNAs (piRNAs) [18][19]. The fundamental sRNA pathway components and other various sRNAs function as critical gene expression regulators to fine-tune the immunity of some cereal plants such as wheat and rice against pathogen invasion [17]. Normally, when a pathogen attacks its host, these sRNAs are either upregulated or downregulated in order to inhibit expression or to release suppression of their targets [5][20]. Thus, plant endogenous sRNAs and sRNA pathway components play key roles in regulating and fine-tuning host immune responses to pathogens such as fungi, bacteria, and oomycetes [21]. Accumulating evidence indicates that sRNAs produced by fungal pathogens can function as effector molecules, modulating host gene expression as a counter-defense mechanism (**Table 1**).

Table 1. Fungal sRNA effectors and their target genes in cross-kingdom interactions.

sRNA	sRNA Origin	Target Origin	Target Genes	Function	Reference
miR408	*Puccinia striiformis* f. sp. *tritici* (*Pst*)	*T. aestivum*	*CLP1*	Negatively regulates host immune response by suppressing the expression of *CLP1*.	[22]
Pst-milR1	*Pst*	*T. aestivum*	*PR2*	Represses plant innate immune response by	[7]

sRNA	sRNA Origin	Target Origin	Target Genes	Function	Reference
				suppressing the expression of *PR2*.	
Pst-milR1	*Pst*	*T. aestivum*	*SM638*	Innate immunity.	[7]
pt-mil-RNA1	*Pt*	*T. aestivum*	*TCP14*, *CYB5R*, and *EF2*	Suppresses wheat defense response to *Pt* by targeting wheat *TCP14*, *CYB5R* and *EF2*.	[18]
pt-mil-RNA2	*Pt*	*T. aestivum*	*TCP14*, *CYB5R* and *EF2*	Suppresses wheat defense response to *Pt* by targeting wheat *TCP14*, *CYB5R* and *EF2*.	[18]
miR398	*Bgh*	Barley	*HvSOD1*	Negatively regulates host immunity by repressing *HvSOD1* accumulation.	[23]
miR9836	*Bgh*	Barley	*MLA1*	Dampens immune response signaling triggered by host MLA immune receptors.	[24]
Fg-sRNA1	*F. graminearum*	Chinese spring wheat	*TaCEBiP*	Suppresses wheat defense response by targeting and silencing *TaCEBiP*.	[25]
Fol-milR1	*Fusarium oxysporum*	*Tomato*	*SlyFRG4*	Suppresses host immunity by silencing *SylFRG4*.	[26]
Osa-miR167d	*M. oryzae*	Rice	*ARF12*, *WRKY45*	Negatively regulates host immunity by downregulating *AR12* expression.	[27]
miR156	*M. oryzae*	Rice	*SPL14*	Enhances host susceptibility by suppressing the expression of *SPL14* and *WRKY45*.	[28]
Osa-miR164a	*M. oryzae*	Rice	*OsNAC60*	Negatively regulates host immunity by suppressing *OsNAC60* expression.	[29]

sRNA	sRNA Origin	Target Origin	Target Genes	Function	Reference
miR168	*M. oryzae*	Rice	*AGO1*	Negatively regulates host immunity by suppressing *AGO1* expression.	[30]
Osa-miR169	*M. oryzae*	Rice	*NF-YAs*	Enhances host susceptibility by suppressing the expression of nuclear factor N-Y (*NF-YA*) genes.	[31]
miR319	*M. oryzae*	Rice	*TCP21*	Negatively regulates host immunity by suppressing *TCP21* expression.	[32]
miR396	*M. oryzae*	Rice	*OsGRFs*	Negatively regulates host immunity by suppressing the expression of *OsGRFs*.	[33]
Osa-miR439	*M. oryzae*	Rice	Predicted target genes *LOC_Os01g23940*, *LOC_Os01g36270*, *LOC_Os01g26340* and *LOC_Os06g19250*	Enhances host susceptibility by suppressing the expression of predicted target genes *LOC_Os01g23940*, *LOC_Os01g36270*, *LOC_Os01g26340* and *LOC_Os06g19250*.	[34][35]
miR444b.2	*M. oryzae*	Rice	MADS-box family genes	Negatively regulates host immunity by suppressing the expression of MADS-box family genes.	[36]
siR109944	*Rhizoctonia solani*	Rice	*FBL55*	Suppresses host immunity to sheath blight.	[37]
Bc-siR3.2	*Botrytis cinerea* (*B. cinerea*)	*A. thaliana*	*MPK1*, *MPK2*	Suppresses *MPK1*, *MPK2* function in plant immunity.	[38]
Bc-siR3.1	*B. cinerea*	*A. thaliana*	*PRXIIF*	Suppresses *PRXIIF* genes.	[38]
Bc-siR3.2	*B. cinerea*	*Solanum*	*MAPKKK4*	Suppresses *MAPKKK4*	[38]

4. Cross-Kingdom RNA Interference during Plant–Fungal Pathogen Interactions

sRNA	sRNA Origin	Target Origin	Target Genes	Function	Reference
		lycopersicum		[40][41] function.	
Bc-siR5	*B. cinerea*	*A. thaliana*	*WAK*	Suppression the function *WAK* genes.	[38]
Bc-siR37	*B. cinerea*	*A. thaliana*	[42][43] *WRKY7*, *PMR6* and *FEI2*	Suppresses plant immunity by repressing the expression of *WRKY7*, *PMR6* and *FEI2.*	[39]

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gh cross-kingdom RNAi [21][44]. sRNAs generated by pathogens and parasites, on the other hand, may also translocate into host cells and induce host gene silencing [38][44][45]. This implies that sRNA transfer is bidirectional; plant-derived sRNAs serve as defense weapons to disrupt fungal pathogenicity genes, while pathogen-derived sRNAs act as offensive weapons to suppress host plant defense mechanisms.

PR2—Pathogenesis-related 2 gene, *TCP14*—Transcription factor, *CYB5R*—Cytochrome b5 reductase, *EF2*—Elongation factor 2, *TaCEBiP*—Chitin elicitor binding protein, *SlyFRG4*—CBL-interacting protein kinase, *MPK*—Mitogen-activated protein kinases, *MAPKKK*—Mitogen activated protein kinase kinase kinase, *PRXIIF*—peroxiredoxin-2F, *WAK*—Cell wall-associated kinase, *PMR*—powdery mildew resistance, *FEI* (named after the Chine

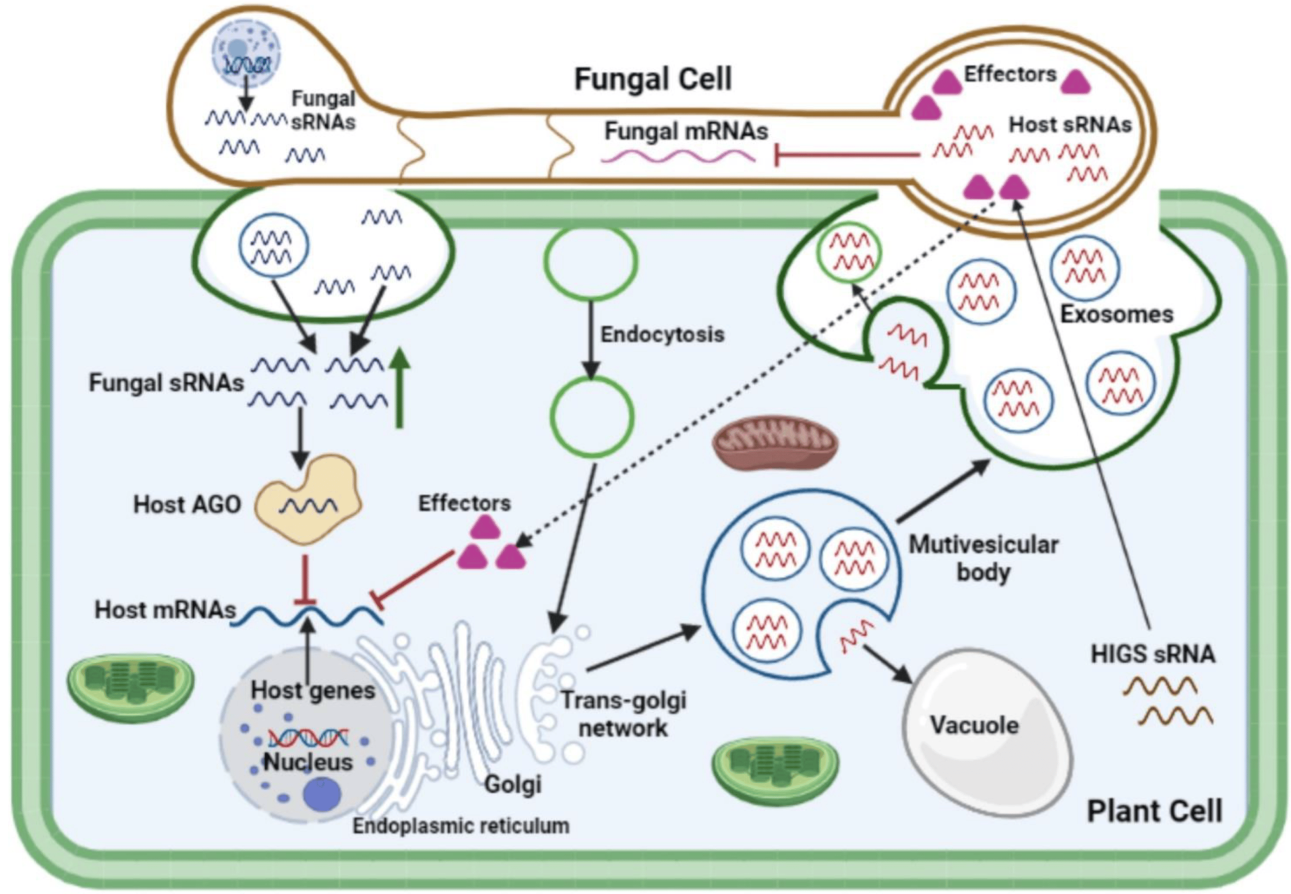

Figure 1. Cross-kingdom RNAi and vesicle trafficking during plant-fungal pathogen interactions. Fungal and plant sRNAs trigger cross-kingdom RNAi during plant-pathogen interactions. Fungal sRNAs translocate into plant cells and hijack the host plant Argonaute (AGO) protein of the RNAi machinery to suppress host plant immune response. The fungal sRNAs are upregulated upon infection (indicated by green arrow). Host cells also can deliver sRNAs into pathogen cell, either host induced gene silencing (HIGS) sRNAs or endogenous sRNAs, to target virulence genes and other essential pathogen genes. The generation of multivesicular bodies and release of exosomes at the site of pathogen invasion is part of the host penetration resistance pathway. Among other

molecules, the putative exosomes contain sRNAs that can target vesicle trafficking components of the pathogen. Exosomes can also inhibit fungal growth and stall further ingress. The production of pathogen-derived sRNAs that may target and silence host genes can be inhibited by this form of host plant immunity. The fungal pathogens also secrete proteinaceous effectors through the haustorium into the host cells to suppress the host immunity genes, thereby causing disease. How fungal pathogens transport proteinaceous effectors and sRNAs into their host cells is still elusive. On the other hand, plants secrete extracellular vesicles to transport host sRNAs into pathogens to silence fungal genes involved in pathogenicity. Passage of host sRNAs through the haustorial cell wall, either active or passive, occurs and once inside the fungal haustorium the silencing molecules trigger RNAi of their mRNA targets, and may act as primers in the fungal silencing pathway, leading to the generation of systemic silencing signals. Cell structures are not drawn to scale.

Since the discovery of RNAi in *Neurospora*, sRNAs from numerous fungal species have been studied [46]. The most well-known example of cross-kingdom RNAi from a plant to its interacting pathogen is HIGS, which occurs when a plant-produced RNAi signal triggers the silencing of a pathogen gene [47]. RNase III-like endonucleases known as Dicers produce sRNAs from hairpin-structured or double-stranded RNA [48]. The mature sRNAs are loaded into AGO proteins to form the RNA-induced silencing complex (RISC) [5][49]. The RISC is responsible for silencing genes that contain sequences complementary to sRNAs. By using the component of the host RNAi machinery known as AGO1, the transfer of *B. cinerea* sRNA into *Arabidopsis* cells silenced the host's immune genes [38]. Fungal sRNAs can suppress host plant immunity by interfering with the RNAi pathways of the host [7][38][39]. During tomato and *Arabidopsis* infection, the most prevalent sRNAs that function as effectors factors to enhance pathogen virulence are *Bc*-siR3.1, *Bc*-siR3.2, and *Bc*-siR3.5 which target the host *mitogen-activated protein kinases MPK1*, *MPK2* and *MPKKK4*, *peroxiredoxin* (*PRXIIF*), and *cell wall-associated kinase* (*WAK*), respectively [38]. These pathogen-derived sRNAs target components of host plant immunity such as oxidative burst and signal transduction pathways; hence, silencing of these targets will enhance pathogen virulence and compromise resistance to the fungal pathogens [38].

A group of fungal in-planta secreted sRNAs was also identified from the sequencing of sRNAs from *Sclerotinia sclerotiorum* during infection of *Arabidopsis* and *Phaseolus vulgaris* [50]. The pathogen-derived sRNAs were predicted to target quantitative disease resistance-associated genes of the host and suppress host plant immunity [50]. Mutations of two sRNA targets that encode kinase genes *SERK2* and *SNAK2* enhanced pathogen virulence and compromised host plant resistance, indicating that the sRNAs' targets are involved in disease resistance [50]. Analysis of *Pst*-infected leaves established that *Pst* is capable of suppressing the host's defense and immunity genes as well as its endogenous genes by producing many sRNAs [6]. Fungal sRNAs can target and silence plant transcripts involved in defense, but sRNAs from plants can target and silence transcripts produced by pathogens [51][52]. A novel *Pst* miRNA (*Pst*-milR1) participates in cross-kingdom RNAi events in wheat by binding the *pathogenesis-related 2* (*PR2*) gene, which may suppress the host-mediated defense mechanism in its counter defense. Silencing of the *Pst*-milR1 precursor using host induced gene silencing resulted in reduced *Pst* virulence and increased wheat resistance to the *Pst* isolate CRY31. Therefore, *Pst*-milR1 is a key pathogenicity factor in *Pst*, which functions as an effector to suppress host immunity [7]. *Fg-sRNA1* produced by *F. graminearum* targets and silences wheat *TaCEBiP* (*Chitin Elicitor Binding Protein*), a pattern recognition receptor gene. *F. oxysporum* f. sp.

lycopersici produces *Fol-milR1*, an sRNA effector that suppresses host immunity by targeting the tomato protein kinase *SlyFRG4* via *AGO4a*, thus providing a novel pathogenicity strategy to achieve infection [26]. Accumulating evidence shows that miRNAs serve crucial roles in regulating the expression of their target genes accurately and effectively during the interactions between rice and *M. oryzae*. Understanding the functions of rice miRNAs is crucial for managing rice blast.

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