CURRENT REVIEW

Host–Pathogen Interaction in *Fusarium oxysporum* Infections: Where Do We Stand?

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Fusarium oxysporum, a ubiquitous soilborne pathogen, causes devastating vascular wilt in more than 100 plant species and ranks 5th among the top 10 fungal plant pathogens. It has emerged as a human pathogen, too, causing infections in immune-compromised patients. Therefore, it is important to gain insight into the molecular processes involved in the pathogenesis of this transkingdom pathogen. A complex network comprising interconnected and overlapping signal pathways—mitogen-activated protein kinase signaling pathways, Ras proteins, G-protein signaling components and their downstream pathways, components of the velvet (*LaeA/VeA/VelB*) complex, and cAMP pathways—is involved in perceiving the host. This network regulates the expression of various pathogenicity genes. However, plants have evolved an elaborate protection system to combat this attack. They, too, possess intricate mechanisms at the molecular level which, once triggered by pathogen attack, transduce signals to activate defense response. This review focuses on understanding and presenting a wholistic picture of the molecular mechanisms of *F. oxysporum*–host interactions in plant immunity.

Fusarium is a cosmopolitan genus of filamentous ascomycete fungi (Sordariomycetes: Hypocreales: Nectriaceae) that resolves into a monophyletic group encompassing all economically important *Fusarium* spp. Nine of the species resolve into 20 monophyletic species complexes that include as many as 60 species. *Fusarium oxysporum* is a ubiquitous, soilborne pathogen which causes devastating vascular wilt in more than 100 plant species and poses a serious threat to a wide range of economically important crops such as banana, cotton, melon, and tomato (Gordon and Martyn 1997) (Table 1). It is considered a species complex in which different species can be pathogenic toward different hosts or nonpathogenic. Isolates pathogenic on the same host are grouped into the same forma specialis (e.g., *F. oxysporum* f. sp. *lycopersici* for tomato pathogens) and the general mode of infection for all formae speciales is similar. Devastating vascular wilt caused by *F. oxysporum* has become a menace to farmers worldwide, curtailing the production of economically important crops. Expanding the host range by horizontal acquisition of

lineage-specific (LS) genomic regions between different species of *F. oxysporum* makes the pathogen even deadlier. It ranks 5th among top 10 fungal plant pathogens (Dean et al. 2012) and has also emerged as a human pathogen (Nucci and Anaissie 2007).

F. oxysporum initially penetrates roots asymptotically. It subsequently colonizes vascular tissue and triggers massive wilting, necrosis, and chlorosis of aerial plant parts. Compared with other *Fusarium* spp., *F. oxysporum* isolates exhibit a high degree of host specificity (Ma et al. 2013). A complex network comprising interconnected and overlapping signaling pathways is activated once *F. oxysporum* recognizes a host in its vicinity. These pathways include mitogen-activated protein (MAP) kinase signaling pathways (Di Pietro et al. 2001), Ras proteins, G-protein signaling components and their downstream pathways (Jain et al. 2002, 2003, 2005; Martínez-Rocha et al. 2008), components of the velvet (*LaeA/VeA/VelB*) complex (López-Berges et al. 2013), and cAMP pathways (Jain et al. 2005). The components of different pathways regulate expression of different pathogenicity genes conferring virulence to *F. oxysporum*.

Some plants have evolved elaborate and sensitive protection systems to combat the attack of *F. oxysporum*, which involve intricate molecular mechanisms that are triggered by pathogen attack and which transduce signals to activate defense responses, as discussed below. Model crops *Arabidopsis thaliana* and tomato have been used as tools to obtain insight into the gene networks that regulate resistance to *F. oxysporum* (Berrocal-Lobo and Molina 2008; Diener and Ausubel 2005). Therefore, effective management of the wilt diseases will require a thorough knowledge and understanding of the molecular mechanisms involved in the pathogenesis of this transkingdom pathogen as well as discerning the nature of resistance in resistant cultivars. This review summarizes aspects of *F. oxysporum* genetics and the plant-signaling networks that successfully circumvent wilt.

PATHOGEN PERCEPTION AND DEFENSE

Plants recognize *Fusarium* attack for effective defense. They have the competence to perceive an arsenal of nonself molecules emanating from *F. oxysporum* as well as endogenous signals originating from their own cell walls by surveillance of cellular intactness. Mechanisms underlying host defense are different in different crops. The plant cell wall is the first barrier that *F. oxysporum* encounters during attack and this barrier defines the primary or basic strength of plants to encounter and restrict it. In some resistant banana varieties, it is the cell wall that imparts resistance to strains of *F. oxysporum* Foc TR4 before colonization (Li et al. 2012). In resistant varieties of banana, the numbers of spores attached to roots are substantially low

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compared with susceptible varieties. Several genes such as 3-deoxy-d-arabino-heptulosonate-7-phosphate synthase, 4-coumarate-CoA ligase, polyphenol oxidase, glutathione S-transferase (GST), UDP-glucuronic acid decarboxylase, and cellulose synthase, which act at different steps of the shikimate phenylpropanoid-lignin and cellulose biosynthesis pathways, are reported to strengthen the cell wall and are upregulated in resistant varieties of banana (Li et al. 2012). The strengthened cell

wall is a possible reason for the reduced spore attachment and enhanced resistance (Li et al. 2012).

Plants recognize microbial surface-derived molecules called pathogen- or microbe-associated molecular patterns (PAMP or MAMP, respectively) through pattern recognition receptors (PRR). Binding of PAMP to distinct PRR activates these receptors and relays the signal downstream to convergent signaling pathways triggering broad-spectrum immunity (Muthamilarasan

Table 1. Some of the major formae speciales of *Fusarium oxysporum*, illustrating its wide host range

Number	<i>F. oxysporum</i>	Crop infected	Symptoms	Reference
1	<i>f. sp. lycopersici</i>	Tomato	Yellow leaves, vascular discoloration, leaf chlorosis and wilted plants	Nirmala-Devi et al. 2016
2	<i>f. sp. melonis</i>	Melon	Yellowing and death of lower leaves, death of branches, brown lesions with dark gum exudates, white mycelial growth on surface of fruit, necrosis, and vine death	Daami-Remadi et al. 2007
3	<i>f. sp. phaseoli</i>	Bean	Wilting, vascular discoloration, chlorosis, dwarfism, premature defoliation, and plant death	Henrique et al. 2015
4	<i>f. sp. radicis-lycopersici</i>	Tomato	Swelling at the crown, orange and brown lesions at the crown, decay and withering of lower stem, root rot, and plant wilting	Can et al. 2004
5	<i>f. sp. cubense</i>	Banana	Reddish-brown discoloration of the rhizome, bright yellow leaves and subsequent collapsing around the pseudostem, and pseudostem wilt	Li et al. 2012
6	<i>f. sp. coglutinans</i>	Cabbage	Yellowing of lower leaves, stunting of plant, distortion of leaves, wilting and death of plant, and vascular discoloration	Reyes and Chadha 1972
7	<i>f. sp. citri</i>	Orange	Discoloration of vascular tissue, root rot in seedlings, wilt, chlorosis, and epinasty of the young leaves (early symptoms). Brown discoloration of vascular tissue, wilting, and death of plant (late symptoms)	Ibtissem et al. 2014
8	<i>f. sp. ciceris</i>	Chickpea	Yellowing and chlorosis of lower leaflets, initial rootlet yellowing followed by gradual browning of roots, retardation of root growth and branching. Chlorosis of aboveground plant parts and wilting	Gupta et al. 2013
9	<i>f. sp. cepae</i>	Onion	Basal and root rot that later spreads to bulb scales	Rabiei-Motlagh et al. 2010
10	<i>f. sp. cannabidis</i>	<i>Cannabis sativa</i>	Foliage turns yellow, wilts, dries up, and hangs on the plants. Dark-brown discoloration of vascular tissue. Infected plants are killed	McCain and Noviello 1985
11	<i>f. sp. canariensis</i>	Date palm	Fronde death from oldest to newest, then frond turns brown or dies, mostly on one side of the rachis (one-sided or both sided). Brown strip on the surface of the petiole or rachis. Longitudinal section of frond has a brown strip externally that will show internal vascular streaking or discoloration	Wang and McKie 2007
12	<i>f. sp. asparagi</i>	Asparagus	Yellow and wilted shoots. Stunted shoot growth and shoot death. Vascular discoloration. Reddish-brown elliptical lesions present at the base of the stem. Cortex with hollow root hypodermis. Brown elliptical lesions at sites of lateral root emergence. Crown exhibits dry-brown rot	Grogan and Kimble 1959
13	<i>f. sp. batatas</i>	Sweet potato	Yellowing of older leaves, transient wilting of vines, stem rot, brown vascular discoloration. Infected sprouts wilt	Hedge et al. 2012
14	<i>f. sp. betae</i>	Sugar beet	Stunted plants, wilted leaves, chlorotic leaves with necrosis at the edges, dried tap root brown to black in color, and plant death	Cramer et al. 2003
15	<i>f. sp. cyclaminis</i>	Cyclamen	Yellowing of leaves on young plants. Wilting and withering of leaves and flowers on mature (flowering) plants. Brown to brownish-black vascular discoloration of roots and tubers. Decaying of older roots and plant death	Pataky 1988
16	<i>f. sp. herbemontis</i>	Grapes	Plant wilting and death, root decay with brown vascular discoloration, pink discoloration in the cortical and vascular tissues, tyloses in the xylem, and rotting of epidermal tissues of the roots. Yellow spots which expand into streaks before leaves die and drop, delayed and weak shoot growth, and low fruit yields	Dore 2009
17	<i>f. sp. dianthi</i>	Carnation	Chlorotic roots and crook neck shoots, leaves and stem wither and turn brown. Brown vascular discoloration that extends into cortex and pith. Shredding of internal tissues	Pennypacker and Nelson 1972
18	<i>f. sp. lactucae</i>	Lettuce	Stunted and chlorotic plants. Death of older leaves and collapse of the entire plant. Taproot turns pink to red in the vascular tissue. Discoloration often extends into the cortex and may be accompanied by extensive rotting	Scott et al. 2010
19	<i>f. sp. gladioli</i>	Gladiolus	Dry corm rot, brownish to black in color. Yellowing and browning of leaves. Premature leaf death	Pataky 1988
20	<i>f. sp. nicotianae</i>	Tobacco	Sudden wilting of one or more leaves on the plant accompanied by yellowing and finally browning and death, wilting, brown vascular discoloration, dry vascular rot, and brittle and achlorophytic leaves	Johnson 1921

(Continued on next page)

and Prasad 2013). These PRR activate the plant's basal immune response by transcribing pathogenesis-related (*PR*) genes and triggering the production of reactive oxygen species (ROS) and other defense metabolites. Release of nonspecific exogenous and endogenous elicitors such as oligomeric or monomeric fragments of both the cuticle and the cell wall elicit innate defense responses and form the first line of defense against *F. oxysporum* (Hückelhoven 2007). Ingress of *F. oxysporum* disrupts pectin

layers and results in release of galacturonic acid-containing fragments. These fragments act as signaling substances that mediate defense response and impart resistance by strengthening defensive barriers (Benhamou et al. 1990). Chitin elicitor-binding protein (CEBiP) and the chitin elicitor receptor kinase (CERK1) are the components of the defense signaling pathway that recognize chitin oligosaccharides, and genes encoding these proteins are upregulated in resistant crop

Table 1. (Continued from previous page)

Number	<i>F. oxysporum</i>	Crop infected	Symptoms	Reference
21	<i>f. sp. narcissi</i>	Narcissus	Stunted, distorted, and yellow shoots. Shoots die prematurely. Stunted roots. Decayed basal plate of bulb with a dry and spongy, chocolate-brown to purplish-brown rot. Decayed bulb with white or pinkish white mold between the scales	Pataky 1988
22	<i>f. sp. medicaginis</i>	Alfalfa	Brown cankerous depressions at the bases of lateral roots, root rot, bright yellow upper leaves which fade to light buff color of dead and bleached alfalfa straw. Basal leaves may have a tinge of old rose or some shade of pink. Tips of the stem droop and wilt, stunting, and plant death	Weimer 1928
23	<i>f. sp. lini</i>	Flax	Collapsing of young seedlings. Rolling and withering of cotyledons, dark green to brown patches appear on leaves followed by shriveling, dropping off, and drying of leaves. Discoloration of the vascular tissues	Kumar et al. 2014
24	<i>f. sp. lentis</i>	Lentil	Severe grain losses, seedling wilt, or adult plant wilt during reproductive growth	Stoilova and Chavdarov 2006
25	<i>f. sp. niveum</i>	Watermelon	Vascular browning of seedlings, wilting of leaflets, and death of seedling. Wilting and death of plant	Dau et al. 2009
26	<i>f. sp. palmarum</i>	Palm	Initially one-sided chlorosis or necrosis of older leaf blades occurs. Reddish-brown stripe appears along the petiole and rachis. Discoloration of internal tissue. Later, entire canopy becomes desiccated and necrotic. Leaves do not droop or hang down around the trunk	Elliott et al. 2010
27	<i>f. sp. pisi</i>	Pea	Pale foliage, downward curling of leaves, and vascular discoloration both below- and aboveground. Above- and belowground vascular system turns light yellow to brick-red color and the lower subterranean portion of the stem becomes larger than normal	Kraft et al. 2000
28	<i>f. sp. passiflorae</i>	Passion fruit	Pale-green leaves exhibiting dieback. Dropping of lower leaves and plant death in young plants. Yellowing of leaves and plant wilt and death in adult plants. Vascular discoloration at root, collar, twig, and stem. Lesions and fissures in collar and stem at high humidity	Joy and Sherin 2012
29	<i>f. sp. perniciosum</i>	Mimosa trees	Linear bark fissures, vascular discoloration, blocked vessels, and lenticular swelling and defoliation	Stipes and Phipps 1975
30	<i>f. sp. ricini</i>	Castor	Gradual yellowing, interveinal necrosis, hang down of leaves, and blackening and necrosis of roots predominantly expressed at flowering and spike formation. Discoloration of young seedlings, black lesions above collar regions in stem, leaves with petiole dry up and hang down. Yellowing, shriveling with marginal and interveinal necrosis of leaves	Dange et al. 2006
31	<i>f. sp. strigae</i>	Striga	Wilting, dieback, necrosis, and chlorosis, browning of the tips of some leaves, and browning of shoots	Endah 2011
32	<i>f. sp. tuberosi</i>	Potato	Dry rot, chlorosis, and wilting	Remadi et al. 2009
33	<i>f. sp. tulipae</i>	Tulip	Leaves turn red, wilt, and die prematurely. Diseased bulbs are dull gray to chalky white in color, have a shrunken basal rot, and fail to sprout. Fewer roots appear on corms	Pataky 1988
34	<i>f. sp. vasinfectum</i>	Cotton	Cotyledon drop, leaf chlorosis and necrosis, plant wilt and death. On older plants, veins are darkened, leaves became partly chlorotic and sometimes abscised. Vascular discoloration usually occurs in the tap root and in the lower part of the stem	Kim 2005
35	<i>f. sp. raphanin</i>	Radish	Yellowing of a single leaf, dark vascular discoloration, root rot, general wilting and dieback of plants	du Toit and Pelter 2003
36	<i>f. sp. fragariae</i>	Strawberry	Reddish-brown discoloration on the crown, drying and early senescence of mature leaves, followed by stunting and wilting of entire plant	Garrido et al. 2016
37	<i>F. oxysporum</i>	Saffron	Infected corms possess dark-brown, sunken, and irregular patches below the corm scales, mostly near root and bud regions. In severe cases, the entire corm turns into a black powdery mass	Husaini 2014

varieties (Li et al. 2012). The phenolic pathway is activated, too, as a part of defense response against cell-wall-derived elicitors from pathogens. Oligosaccharide derivatives of *F. oxysporum* (α -D-mannopyranosyl-[1-2]- α/β -D-glucopyranosyl and α -D-mannopyranosyl inositol) induce phenylalanine ammonia lyase activity (Nita-Lazar et al. 2004). Several defense genes such as thionins like *Thi2.1* (small, basic, cysteine-rich antimicrobial proteins), *PR-1* and *PR-5* genes, as well as the plant defensin gene *Pdf1.2* are induced in *Arabidopsis* plants following infection by *F. oxysporum* (Epple et al. 1997).

HOST PERCEPTION AND VIRULENCE

Perception of the host is a prerequisite for vascular infection by *F. oxysporum*. The pathogen recognizes suitable hosts, and penetrates and invades plant tissues (Michiels et al. 2009). It successfully circumvents plant nonself-recognition and basal defense during penetration. Dihydroxy-C16 and trihydroxy-C18 acids, characteristic hydroxy acids unique to cutin, act as specific inducers, giving the fungus a failsafe method of sensing that it is in contact with the plant (Woloshuk and Kolattukudy 1986). *Fusarium* spp. perceive chemical and physical signals from the host and respond with the appropriate metabolic and morphogenetic changes required for pathogenic development. Also, host-derived hydrolases, including chitinases and glucanases, release monomers that act as elicitors, conveying a signal to the fungus for the synthesis of enzymes (cutinases, pectinases, endopolygalacturonases, and other hydrolytic enzymes) required for host penetration (Woloshuk and Kolattukudy 1986).

Different signaling cascades are activated in *Fusarium* spp. during host infection. Their activation mainly depends on the perception of signals by different receptor proteins, usually at

the cell surface, which bind the signal molecule. Membrane proteins Msb2 and Sho1 regulate the infection processes in *F. oxysporum* (Fig. 1A). Msb2, a highly glycosylated transmembrane protein, and Sho1, a tetraspan transmembrane protein, contribute to plant infection by regulating the Fmk1 pathway. Required for full phosphorylation of Fmk1, Msb2 and Sho1 together function upstream of Fmk1. Msb2 and Sho1 contribute to virulence in several ways: they (i) upregulate Fmk1-regulated genes encoding different enzymes involved in cell wall biogenesis, (ii) contribute to cell wall stress response, and (iii) promote Fmk1-dependent virulence functions. Together with Fmk1, these membrane proteins (Sho1 and Msb2) are required for upregulation of *chsV*, *fks1*, and *gas1* genes involved in cell wall biogenesis (Pérez-Nadales and Di Pietro 2011, 2015).

RHO-type GTPase Rho1 of *Fusarium* spp. is required for the correct assembly of the cell wall and for virulence (Fig. 1A). Rho1 positively regulates posttranslational activity of glucan synthase and plays an important role in maintaining the hyphal architecture, which prevents its detection by the host (Martínez-Rocha et al. 2008). GTP-binding proteins are essential components that mediate cellular responses to environmental stimuli. When an extracellular signal molecule binds to a G protein coupled receptor, the receptor undergoes a conformational change that enables it to activate a trimeric GTP-binding protein (G protein). The G protein is attached to the cytoplasmic face of the plasma membrane, and is composed of three protein subunits: α , β , and γ . *F. oxysporum* possesses genes encoding G α proteins FGA1 and FGA2 and G β protein FGB1. FGA1 and FGA2 regulate adenyl cyclase activity and alter cAMP levels, which result in pathogenicity (Jain et al. 2002, 2003, 2005) (Fig. 1F). Disruption of *FGA1* and *FGA2* leads to reduced pathogenicity and alterations in colony morphology.

Fig. 1. Pictorial representation of the major players in the *Fusarium oxysporum* infection process.

SIGNALING IN THE PATHOGEN

Stimulation by a signal initiates a specific signal transduction pathway. The three-component MAP kinase module processes the signals inside the receiving cell and distributes it to the appropriate intracellular targets (Fig. 1A and B). The first module of this cascade, MAP kinase kinase kinase, phosphorylates and, thereby, activates MAP kinase kinase which, in turn, phosphorylates and activates MAP kinases (MPK). Once activated, the MPK relay the signal downstream by phosphorylating various proteins in the cell, including gene regulatory proteins and other protein kinases (Widmann et al. 1999).

MPK play a fundamental role in determining virulence of *F. oxysporum*. These MPK channel information required for imparting full virulence. There are various MPK that regulate virulence in *F. oxysporum*, some of which have been studied in detail while some are yet to be studied. MPK Fmk1, belonging to the yeast and fungal extracellular signal-regulated kinase (YERK1) subfamily, is indispensable for virulence of *F. oxysporum*. Fmk1 is an important component of the signal transduction pathway that regulates various infection processes of *F. oxysporum* such as adhesion of *F. oxysporum* to roots of host formation of infection hyphae, root attachment and penetration, vascular colonization, and invasive growth on the living plant tissue. Fmk1 also plays an important role in maceration of the fruit tissue in tomato fruit and production of aerial mycelium on its surface (Di Pietro et al. 2001). Fmk1 regulates expression of several genes such as endo-pectate lyase *pl1*, *chsV*, *fks1*, and *gas1*. The reduced expression of these genes in *fmk1* mutants explains the inability of *F. oxysporum* to cause pathogenicity (Nadalez and Di Pietro 2014).

Histidine kinase Fhk1 is another key element that contributes to virulence, oxidative stress, and fungicide sensitivity by recruiting several signaling pathways. Fhk1 regulates postpenetration events and enhances disease symptoms (Rispaal and Di Pietro 2010). Fhk1 controls stress adaptation, partly by recruiting an MPK Hog1 and partly by inhibiting Fmk1 that acts as a negative regulator of oxidative stress response. Activation of Fhk1 is followed by recruitment of the Hog1 pathway in *F. oxysporum* (Fig. 1B).

F. OXYSPORUM VIRULENCE

Genetic regulation.

Genetic regulation of virulence in *F. oxysporum* is quite complex, with a number of genes regulating virulence. *F. oxysporum* f. sp. *lycopersici* strain 4287 genome size is 61 Mb and comprises 17,735 genes distributed over 15 chromosomes (Ma et al. 2013). The genome is compartmentalized into two regions: the core genome responsible for primary metabolism and reproduction and the adaptive genome responsible for pathogen virulence (Ma et al. 2013). Genes involved in virulence and host specialization are located on pathogenicity chromosomes (Ma et al. 2013). Genome comparison of pathogenic *F. oxysporum* formae speciales virulent on tomato reveal horizontal acquisition of LS genomic regions within them. These LS regions include four entire chromosomes (chromosomes 3, 6, 14, and 15) and parts of chromosome 1 and 2 (Ma et al. 2010; Niño-Sánchez et al. 2016). These regions possess a surprising enrichment of transposable elements as well as *SIX* genes (Houterman et al. 2008; Rep et al. 2004). Colonization of the tomato xylem system is associated with the secretion of SIX proteins. Genes for Six1 (*avr3*), Six3 (*avr2*), Six5, Six6, and Six7 as well as a gene encoding the in planta secreted oxidoreductase (ORX1) are all located on chromosome 14. This chromosome is present in all pathogens causing tomato wilt but absent in avirulent strains, suggesting its horizontal acquisition

(Ma et al. 2010). The mobilization of these LS chromosomes by avirulent *Fusarium* spp. may lead to rapid emergence of new pathogenic lineages (Ma et al. 2010).

Recently, 61 complete mitogenomes of *F. oxysporum* species complex strains were de novo assembled and annotated, which resolved them into three phylogenetic species (Brankovics et al. 2017). Comparative analysis revealed that recombination takes place within the phylogenetic species, indicating presence of a parasexual cycle in *F. oxysporum*.

The *FRP1* gene, encoding a protein with a conserved F-box motif, plays an important role during the first phase of infection. In addition, the fungal genes *ARG1* (encoding arginine-succinylase) (Namiki et al. 2001), *Fow1* (encoding a mitochondrial carrier protein) (Inoue et al. 2002), *Fow2* (encoding a Zn[II]2Cys6 transcription regulator), and *SNF1* (sucrose nonfermenting) collectively contribute to pathogenicity. Furthermore, the *Clc1* gene (encoding a chloride channel) regulates laccase activity and virulence in *F. oxysporum* (Canero and Roncero 2008). Members of Velvet complex VeA, VelB, and VelC positively regulate developmental processes such as hyphal growth, asexual sporulation, and conidial growth. The Velvet complex remodels chromatin and promotes its accessibility at target loci, facilitating expression of the biosynthetic gene cluster for beauvericin (Fig. 1K). The exact mechanism of chromatin remodeling remains to be elucidated (López-Berges et al. 2013).

The presence of an intact fungal cell wall is essential for fungal pathogenicity. The genes that confer this pathogenicity trait in *F. oxysporum* are those encoding chitin synthase V, mannose-6-phosphate isomerase, and *DCWI* (Michielse et al. 2009). Peroxin genes *PEX1*, *PEX10*, *PEX12*, and *PEX26* encoding four peroxins involved in docking and translocation of receptor-cargo moieties across the peroxisomal membrane also contribute to pathogenicity (Michielse et al. 2009). Large-scale insertional mutagenesis of *F. oxysporum* genome carried out by Michielse et al. (2009) revealed that a number of pathogenicity genes influence successful colonization of plant tissues such as chitin synthase V (*chsV*), vitamin B6 metabolism protein (*FOXG_08652*), a GTPase-activating protein (*FOXG_07699*), an RNA polymerase II transcription mediator (*FOXG_08531*), and a Ca²⁺ permease/membrane transporter involved in calcium homeostasis (*FOXG_11097*). In addition, the results of insertional mutagenesis reveal that genes encoding components of amino acid and lipid metabolic pathways, cell wall integrity, protein translocation, and degradation may have a function in vegetative growth and, thus, influence the pathogenicity of *F. oxysporum*, too. Some of these genes are present as multiple copies in the genome of *F. oxysporum* (i.e., chitin synthase V, developmental regulator FlbA, carboxy-cis,cis,muconate cyclase, and transcription factor Fow2).

Transcriptional regulation.

Virulence in *F. oxysporum* is a polygenic trait that is governed by transcriptional regulation of many genes and the transcriptional factors regulating their expression. Each of these genes contributes to virulence and, collectively, they govern the virulence of *F. oxysporum*. These genes encode various components of different pathways that sense the host plant and encode products that play important roles in virulence. The expression of these genes is regulated by a complex array of transcriptional factors. There are seven transcriptional regulators described for virulence in *F. oxysporum*, as follows. (i) Con7-1 is an important transcription factor that regulates vital processes of morphogenesis in *F. oxysporum*-like cell-wall biogenesis, cell division, and differentiation of infectious structures. Con7-1 possess a nuclear localization signal, a Cys₂His₂ DNA-binding domain, a coiled-coil region responsible for

protein–protein interactions, and a proline/glutamine-rich C terminal transactivation domain. *Con7-1* regulates expression of several genes encoding proteins such as endopolygalacturonases, cellulases, and Six proteins (Ruiz-Roldan et al. 2015) (Fig. 1G and H). (ii) *Sge1* regulates the expression of *SIX* genes and is required for colonization of the xylem system and disease development (Michielse et al. 2009). *Sge1* expression, in turn, is regulated by *FTF1* and *FTF2* transcription factors (Niño-Sánchez et al. 2016). (Fig. 1H). (iii) *Ftf1* encodes yet another important transcription factor that positively regulates virulence during early stages of infection (Ramos et al. 2007; van der Does 2016). (iv) *Ste12* encodes a homeodomain transcription factor that regulates invasive growth downstream of the Fmk1 pathway (Rispaill and Di Pietro 2009). (v) *XlnR* encodes a major transcriptional activator of xylanase genes *xly3*, *xly4*, and *xly5* regulating the expression of these plant cell-wall-degrading enzymes (Calero-Nieto et al. 2007) (Fig. 1I). (vi) Transcriptional factor encoding genes *ctf1* and *ctf2* regulate the expression of genes encoding cutinases and lipases (Bravo-Ruiz et al. 2013). (vii) Finally, *pacC* encodes a transcription factor that acts as a negative regulator of virulence by repressing expression of acid-expressed virulence genes and polygalacturonases *pg1* and *pg5* (Caracuel et al. 2003) by binding the consensus sequence 5'-GCCAAG-3' (Fig. 1J).

Nitrogen sources and virulence.

Nitrogen-containing metabolites are a key signal that regulates expression of virulence genes in *F. oxysporum*. Preferred nitrogen sources are readily assimilated compounds such as ammonium or glutamine. Their presence causes nitrogen catabolite repression, whereby genes required for exogenous nitrogen source utilization are downregulated (Marzluf 1997; Wong et al. 2008). As such, infection-related functions (cellophane invasion), vegetative hyphal fusion, and root adhesion are repressed (in *F. oxysporum*). Transmission of the repressing signal requires conserved Ser/Thr kinase TOR and the bZIP transcriptional regulator MeaB (Fig. 1E). Glutamine synthase phosphorylates TOR. TOR transmits its signal to MeaB and negatively regulates transcription of virulence genes. AreA, belonging to the GATA binding family of transcription factors, acts as an activator of nitrogen catabolic genes whereas MeaB mediates repression of nitrogen catabolic genes but both regulators act as repressor of virulence functions. MeaB and AreA repress expression of the Ste12 transcriptional regulator of the Fmk1 pathway (López-Berges et al. 2010). The nitrogen response pathway and Fmk1 pathway are antagonistic in action. The Fmk1 pathway positively regulates expression of virulence genes whereas the preferred nitrogen source represses virulence genes.

HOST RESISTANCE

Transcription factors.

Transcription factors in the host play an important role as positive and negative regulators of antimicrobial compounds during *F. oxysporum* infection. One among these is ATAF2, which belongs to the NAC protein family and increases susceptibility to *F. oxysporum*. Its overexpression in *Arabidopsis* reduces resistance to *F. oxysporum*. It functions as a repressor of Fox-inducible defense response in *Arabidopsis*. ATAF2 expression responds to jasmonic acid (JA) and salicylic acid (SA) treatment and its gene product blocks the expression of Fox-inducible defense genes plant defensin1.2 (*PDF1.2*) and *PR1* (Berrocal-Lobo and Molina 2008). Similarly, overexpression of transcription factors *ERF4* and *WRKY70* also leads to decreased resistance against *F. oxysporum* (Berrocal-Lobo and Molina 2008). In contrast, overexpression of *ERF1*,

ERF2, and *ERF14*, which encode proteins belonging to the APETALA/ethylene (ET)-responsive-element binding protein (EREBP) family, imparts resistance against *F. oxysporum*. Induction of *ERF1* and *ERF2* depends on *ERF14*. These transcription factors are involved in ET and JA signaling. ERF72, another transcription factor belonging to the AP2/ERF family, suppresses programmed cell death and regulates expression of *PDF1.2* and *GST6* (Ogawa et al. 2005). There are some transcription factors whose role remains to be elucidated. *MYB122*; *ANAC03* and -42; *AtbHLH038* and -039; and *WRKY45*, -51, -53, -63, and -75 are all induced at early and late stages of *F. oxysporum* infection. *MYB15* and -51 are induced at an early stage only, whereas *ERF1* and *ANAC019* are uniquely induced at late infection stages (Zhu et al. 2013). *MYB51* has a role in regulating biosynthesis of antimicrobial substances, while *ANAC019* regulates JA-signaled defense response downstream of *MYC2* (Bu et al. 2008).

Genes.

Several genes responsive to *F. oxysporum* infection have been identified thus far. These include genes involved in biosynthesis of JA, indole glucosinolate, camalexin, and callose (Bednarek et al. 2009; Clay et al. 2009; Kidd et al. 2011; Liu et al. 2010; Manzo et al. 2016; Pfalz et al. 2009; Zhu et al. 2013). Also responsive to *F. oxysporum* infection are genes encoding dirigent-like protein (At1g64160), germin-like protein (At1g18970), CAP family protein (cysteine-rich secretory proteins, antigen 5, and PR1) (At4g33720), and wound-responsive family proteins (At4g10270 and At4g33560). The genes which are significantly upregulated in *F. oxysporum*-infected *Arabidopsis* plants include those involved in the biosynthesis pathways of tryptophan, indole-3-methyl-glucosinolate, and camalexin (Kidd et al. 2011).

The role of resistance (*R*) genes conferring *F. oxysporum* immunity is quite significant. These genes confer resistance against *F. oxysporum* that express the corresponding avirulence (*Avr*) gene. Dominant plant *R* genes against different races of *F. oxysporum* have been identified in several crops (Dean et al. 2012). Interaction between *F. oxysporum* sp. *lycopersici* and tomato is race or cultivar specific. Immunity to *F. oxysporum* sp. *lycopersici* was first found in Missouri accession 160 (*Lycopersicon pimpinellifolium* PI79532) and the symbol *I* was used to denote the factor (gene) of immunity (Huang and Lindhout 1997). There are three races of this pathogen (races 1, 2, and 3), of which race 3 is the most devastating. Corresponding to these races, three loci (*I-1*, *I-2*, and *I-3*) which confer resistance in tomato were identified earlier (Panthee and Chen 2010). All commercially cultivated tomato lines (*L. esculentum*) lacking *I* genes are susceptible to *F. oxysporum* sp. *lycopersici*. The literature is confusing with regard to the use of the gene symbol *I* and *I-1* for race 1 resistance. At present, most researchers use *I* when the resistance in *L. pimpinellifolium* is concerned and *I-1* when the resistance is derived from other sources such as *L. pennellii* (Huang and Lindhout 1997). *R* genes against *F. oxysporum* sp. *lycopersici* have been characterized and mapped to three clusters on chromosome 7, 8, and 11 of tomato (Gonzalez-Cendales et al. 2016). *I* and *I-2* have been mapped on chromosome 11 (Laterrot 1976; Paddock 1950), *I-1* and *I-3* on chromosome 7 (Bournival et al. 1989; Hemming et al. 2004; Sarfatti et al. 1991), and *I-7* on chromosome 8 (Gonzalez-Cendales et al. 2016). Actually, *I-3* and *I-7* genes for resistance to *F. oxysporum* sp. *lycopersici* race 3 were identified in *L. pennellii* from accessions LA716 (Scott and Jones 1989) and PI414773 (McGrath et al. 1987) but both genes were designated *I-3*. However, gene mapping revealed that the two genes were not the same (Lim et al. 2006). The *I-3* gene from LA716 encodes an S-receptor-like kinase (SRLK) protein

(Catanzariti et al. 2015; Lim et al. 2008), while *I-7* encodes a leucine-rich repeat (LRR) receptor-like protein and, unlike *I-3* (and *I-2*)-mediated resistance, it is not suppressed by *Avr1* (Gonzalez-Cendales et al. 2016). Using transgenic tomato plants carrying only the *I-7* gene for *F. oxysporum* sp. *lycopersici* resistance, Gonzalez-Cendales et al. (2016) found that *I-7* also confers resistance to *F. oxysporum* sp. *lycopersici* races 1 and 2. A submember of the *I-2* locus (*I-2C-5*), belonging to the nucleotide-binding site (NBS)-LRR family of resistance genes, has also been shown to confer partial resistance in transgenic plants (Sela-Buurlage et al. 2001). The *R* gene *I-3* confers recognition of the *SIX1* gene product of *F. oxysporum*, which encodes a cysteine-rich protein (Rep et al. 2004). *Six-1* loci (1 for “immunity to Fusarium wilt”) confer partial resistance to different *F. oxysporum* sp. *lycopersici* races and the locus *I-2* confers complete plant resistance to specific races of Fox. Some genes of *SIX-1* loci encode resistance proteins of the NBS-LRR subclass (Berrocal-Lobo and Molina 2008), today called nod-like receptors (NLR). In *Arabidopsis*, several NLR-encoding genes (*At1g57630*, *At3g04220*, and *At4g11170*) of the Toll interleukin-1 receptor class are also induced following *F. oxysporum* infection (Zhu et al. 2013).

Several receptor-like kinases (RLK) are also implicated in *F. oxysporum* resistance. *Arabidopsis* has six dominant resistance loci to *F. oxysporum*. Among them, *RFO1* is the largest contributor to resistance and offers resistance toward three *F. oxysporum* species. *RFO1/WAKL-22* encodes a wall-associated RLK (WAK) and confers broad resistance interdependent on *RF02*, *RF04*, and *RF06* (Diener and Ausubel 2005). Some RLK genes (*At3g59700*, *At5g01540*, *At5g60900*, *At1g65790*, *At4g13920*, *WAK1*, *WAK3*, and *WAKL10*) are also induced upon *F. oxysporum* infection in *Arabidopsis*. It seems that plants may use these receptors to detect multiple elicitors released by *F. oxysporum* (Zhu et al. 2013).

Defense molecules and hypersensitive response.

Plants are equipped with defense molecules against *F. oxysporum*. These defense molecules can kill their target pathogen through their precise defense signaling approaches. α -Tomatine, a glycoside lycotetraose, is a major saponin in tomato that has fungicidal action on certain strains of *F. oxysporum*. Elucidation of the mode of action of α -Tomatine reveals that it induces cell death by activating a Tyr kinase and its downstream targets, a farnesyl transferase and the mitochondrial ATP synthase F_0F_1 -ATP, leading to intracellular Ca^{2+} elevation and the oxidative burst. Cross talk between Tyr phosphorylation and Ras pathways also takes place (Fig. 1D) (Ito et al. 2007). NAD1, an antifungal plant defensin, kills *F. oxysporum* by binding to the cell wall of hyphae, followed by permeabilization of the fungal plasma membrane via the formation of an aperture and induction of ROS production via unknown pathways, ultimately causing cell death (Fig. 1C) (van der Weerden et al. 2008).

The second layer of defense is the hypersensitive response (HR), which is characterized by the accumulation of ROS during the oxidative burst, and the accumulation of antimicrobial proteins and phytoalexins. These immune responses culminate in a local, cellular suicide associated with restricting the spread of pathogens. ROS are induced by either cell wall peroxidases or plasma membrane NADPH oxidases. Peroxidase-dependent ROS production has been observed in *Arabidopsis* cell suspension cultures in response to *F. oxysporum* elicitors (Davies et al. 2006). *F. oxysporum*-derived elicitor necrosis and ET-induced peptide 1 (Nep1) generates NADPH oxidase-dependent ROS. Expression of genes encoding NADPH oxidases such as *AtRBOH-A*, *-B*, and *-D* are significantly upregulated upon exposure to Nep1 (Bae et al. 2006; Zhu et al. 2013). NADPH oxidases are also upregulated in cotton, wheat, banana, and cucumber after infection by *F. oxysporum* (Dowd et al. 2004; Li

et al. 2012). However, how these oxidases impart basal resistance or are involved in the HR to *F. oxysporum* remains unclear.

Another defense system that operates in plants is systemic acquired resistance, which is activated by hormones, mostly SA (Chen et al. 2014). It has been proposed that resistance to *F. oxysporum* is mediated mainly by JA and ET signaling pathways (Li et al. 2012). Genes responsive to ET stimulus are activated early during infection. High transcriptional levels of genes encoding ET-insensitive 3 and ET-insensitive 3-like 1 were observed in a resistant variety of banana during early stages of *F. oxysporum* challenge. In contrast, genes involved in JA metabolism and signaling, as well as genes responsive to SA and abscisic acid, are activated later. Levels of core JA-signaling component jasmonate ZIM motif proteins, TIFY10B-like gene, and a jasmonate-inducible protein (the extracellular superoxide dismutase $[Cu-Zn]^{2+}$), were found to be high in roots of the resistant banana variety, supporting the notion that JA plays a positive role in imparting resistance to *F. oxysporum*. The high expression levels of genes encoding lipoxygenase-like and allene oxide synthase also suggest that JA levels are quite high in resistant varieties (Li et al. 2012; Zhu et al. 2013). Despite the fact that levels of JA are high in resistant varieties, a role of JA is somewhat controversial. Some studies reported that the JA coreceptor COI1 and JA-associated gene expression pathways involving *MYC2* and *PFT1* impart susceptibility to *F. oxysporum* (Anderson et al. 2004; Kidd et al. 2009; Thatcher et al. 2009). Other studies indicated that *F. oxysporum* manipulates the JA signaling pathway for disease progression. Indeed, JA signaling components predispose plants to *F. oxysporum* as well as suppress MAMP responses (Chen et al. 2014). Detailed studies that elucidate the exact role of these hormones in disease resistance remain to be carried out.

Noncoding RNA.

Noncoding RNA (ncRNA) play an important role in a wide range of biological processes, including response to biotic or abiotic stresses. They are categorized as short ncRNA (<200 bp) and long ncRNA (lncRNA; >200 bp) based on their lengths. Thus far, 15 long noncoding natural antisense transcripts (lncNAT) and long intergenic ncRNA (lincRNA) and 20 novel intergenic transcriptionally active regions responsive to *F. oxysporum* infection have been identified in *Arabidopsis*. Of these, five lincRNA play important roles in defense against *F. oxysporum* infection (Zhu et al. 2014). The most significantly induced lncNAT is *At1g13609*, while *F. oxysporum*-induced antisense transcription was also seen for *At1g13607* and *At1g13608*. These three genes are clustered together in a 2.5-kb region on chromosome 1, and belong to a small clade of the defensin-like protein family (Silverstein et al. 2005).

F. oxysporum infection leads to change in miRNA levels. Ten microRNA (miRNA), belonging to eight families, are up- or downregulated at different time points following *Fusarium* infection of *Arabidopsis*. miRNA *miR159b* slightly induces expression levels of its target genes *MYB33* and *MYB65*. Similarly, the enhanced expression of *MIR398b* and *MIR398c* during late stages downregulates their target genes, particularly the gene encoding copper superoxide dismutase2 (*CSD2*), suggesting the possible role of *miR398*-mediated regulation of *CSD* genes in a defense network against *F. oxysporum* infection (Zhu et al. 2013).

SUMMARY

The emergence of *F. oxysporum* as a deadly vascular wilt fungus can be attributed to the collective contribution of individual genes which encode different receptors that sense

the host, MAP and His kinases that relay the message onward, transcriptional regulators of genes encoding virulence products, and pathogenesis genes. Extensive research has been conducted to elucidate the complexity of the signaling pathways and transcriptional regulation of virulence genes involved in pathogenicity of *F. oxysporum*. However, there are loopholes and gaps in the complete picture. Proteomic studies can help fill these loopholes and gaps. Expressional proteomics can significantly contribute to the analysis of global changes in protein expression of resistant and susceptible cultivars under *F. oxysporum* attack. In addition, it can also analyze the proteome of pathogenic and nonpathogenic races of *F. oxysporum* when they attack the same host. Different post-translational modifications related to alterations in the “host proteomic profile” in response to *Fusarium* infection can also be elucidated. The chemical proteomic based novel technique activity-based protein profiling can help reveal the role of “active” proteins involved in such interactions. There are probes available for different classes of active proteins such as serine hydrolases, cysteine proteases, glucosidases, and so on. Experiments involving such fluorescent probes display remarkably different profiles upon *F. oxysporum* infection in saf-fron. Activities of putative α -glucosidase (100 kDa) and putative β -glucosidases (50 to 70 kDa) are increased, whereas the activity of one strong 50-kDa and several 60-kDa weaker serine hydrolase signals is reduced upon infection. The activity profile of cysteine proteases representing papain-like cysteine proteases or vacuolar processing enzymes changes dramatically, too (Husaini et al. 2018). Metabolomic profiling of the fungus can further narrow the gap of understanding as the fine tuning of different networks that render *F. oxysporum* deadly finally culminate into metabolic products.

Exploitation of this repertoire of knowledge can assist us in development of crop varieties that can resist fungal attack by approaches like RNAi to silence essential genes such as the ones that prevent detection of the fungus by cognate receptors of the host or disruption of receptors which lead to reduced pathogenicity. We could also explore the possibilities of multiplex genome editing of *F. oxysporum* with CRISPR/Cas9. Transgenic plants expressing the cas9 protein and multiple sgRNA targeting genes vital for *F. oxysporum* pathogenesis can be generated, and this could successfully circumvent the proliferation of the pathogen within host tissues. MAP and His kinases, downstream regulators, or master regulators that regulate expression of various virulence genes can also be targeted by synthetic or plant-based molecular inhibitors acting like fungicides. Other questions need to be addressed, such as which elicitors induce the ROS burst in resistant varieties and why preferred nitrogen sources repress virulence.

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