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SI PLANT BIOTIC INTERACTIONS

Tools of the crook- infection strategies of fungal plant pathogens

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SUMMARY

Fungi represent an ecologically diverse group of microorganisms that includes plant pathogenic species able to cause considerable yield loses in crop production systems worldwide. In order to establish compatible interactions with their hosts, pathogenic fungi rely on the secretion of molecules of diverse nature during host colonization to modulate host physiology, manipulate other environmental factors or provide self-defence. These molecules, collectively known as effectors, are typically small secreted cysteine-rich proteins, but may also comprise secondary metabolites and sRNAs. Here, we discuss the most common strategies that fungal plant pathogens employ to subvert their host plants in order to successfully complete their life cycle and secure the release of abundant viable progeny.

Keywords: fungus, plant pathogen, effector, host immunity, virulence.

INTRODUCTION

Fungi constitute an evolutionarily and ecologically diverse group of microorganisms that includes plant pathogenic species that cause considerable yield losses in agricultural production systems worldwide. Generally, the lifestyles of plant pathogenic fungi are differentiated depending on the strategies used to acquire nutrients from their hosts. As such, obligate biotrophic fungi comprise those species that can only feed on living host tissue to meet their nutritional requirements and complete their life cycle. At the complete opposite of the spectrum, necrotrophic fungi trigger cell death in the host to secure nutrient supply. In between these extremes is a wide array of hemibiotrophic fungi that start their compatible host interaction with an initial biotrophic phase that, at one point in time when the infection progressed sufficiently, is followed by a transition to a necrotrophic stage. A parasitic lifestyle that involves the extraction of sugars from other organisms is one of the ways in which non-heterotrophic organisms compensate for the inability to generate sugars through photosynthesis. Many biotrophic and hemibiotrophic fungi evolved haustoria, appendages of fungal hyphae that invaginate the host plasma membrane and grow inside host cells, to obtain these nutrients. Recently, it was demonstrated that the obligate biotrophic powdery mildew fungus *Golovinomyces cichoracerum* requires lipids for colonization that it receives from the host plant (Jiang *et al.*, 2017).

Lifestyle differences largely determine the wide array of strategies that fungi use to evade, counteract or hijack plant defences in their effort to complete their life cycle and secure the production of viable progeny. Irrespective of their lifestyle, microbial pathogens are all believed to utilize so-called effectors, *in planta*-secreted molecules of various nature, to support host colonization, often, but not exclusively, through suppression of host immune responses (Rovenich *et al.*, 2014). Over the years it has become evident that haustoria are not only fungal feeding structures, but are also active sites for secretion and translocation of effectors into the host (Mendgen and Hahn, 2002; Whisson *et al.*, 2007; Rafiqi *et al.*, 2010, 2012).

Plants have developed an innate immune system to recognize and respond to microbes (Thomma *et al.*, 2001; Jones and Dangl, 2006; Cook *et al.*, 2015; Figure 1). This immune system relies on the presence of immune receptors that detect pathogen invasion through sensing of pathogen(-induced) ligands, collectively termed invasion patterns, to mount appropriate immune responses (Cook

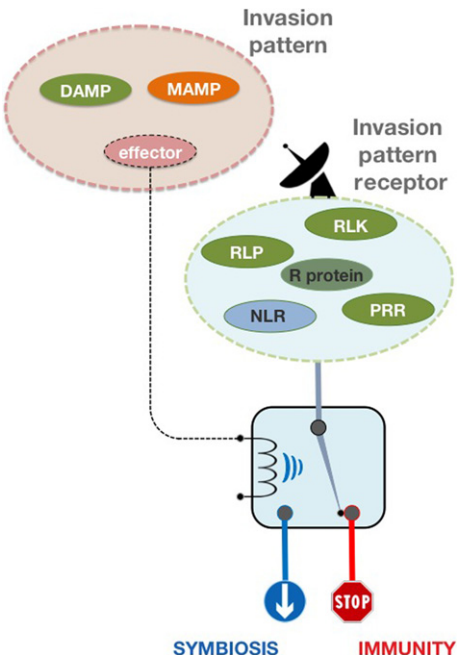

Figure 1. Schematic representation of the 'Invasion Model' to describe the molecular basis of plant immunity against fungal pathogens.
In this model, invasion pattern receptors, comprising any type of host receptor, detect invasion patterns, comprising externally encoded and modified-self ligands that announce invasion, to mount an effective immune response and halt the symbiosis. Fungal effectors may manipulate the induced response to tweak the symbiosis to their benefit.

et al., 2015). Recognition of invasion patterns triggers both local and systemic reactions to respond in a quick and focussed manner to attempted microbial ingress (Thomma *et al.*, 2001; Jones and Dangl, 2006; Cook *et al.*, 2015). For example, the well-characterized invasion pattern chitin, an important constituent of fungal cell walls, is recognized by plants through plasma membrane-localized extracellular lysin motif (LysM)-containing receptor molecules (Felix *et al.*, 1993; Shibuya *et al.*, 1993). Pathogen recognition by plant immune receptors causes ion fluxes, the accumulation of reactive oxygen species (ROS), and a quick activation of defence-related mitogen-activated protein kinase (MAPKs) cascades that cause an extensive transcriptional reprogramming of the host (Altenbach and Robatzek, 2007; Boller and Felix, 2009; Bolton, 2009). Furthermore, pathogen perception leads to reinforcement of plant cell walls by callose deposition, changes in hormone biosynthesis and the production of antimicrobial compounds (Macho and Zipfel, 2014). In many cases, these defence responses collectively are sufficient to render the interaction between the plant and the invader incompatible, implying that pathogen ingress is halted or at least significantly slowed down. However, co-evolutionary processes have selected pathogens that employ a plethora of virulence strategies to overcome various mechanisms within plant immune systems. In this review, we summarize the different virulence strategies that plant pathogenic fungi use to subvert their hosts. While there are excellent reviews that discuss individual strategies in detail, the aim of this review is to outline the broad diversity of known fungal virulence mechanisms (Figure 2).

Fungal strategies for host penetration

One of the first barriers that fungal pathogens have to breach to gain entrance to their hosts is cell walls that are mainly composed of carbohydrates. Many plant pathogenic fungi utilize specialized infection structures, called appressoria, to generate focused turgor pressure to breach the cell wall by force (Ryder and Talbot, 2015). Depending on the fungal species, the turgor pressure is combined with the localized release of cell-wall-degrading enzymes (CWDEs; Ryder and Talbot, 2015). Furthermore, effectors are secreted from appressorial penetration pores prior to host invasion (Kleemann *et al.*, 2012).

Fungi typically produce an arsenal of so-called carbohydrate-active enzymes (CAZymes) that are grouped into five enzyme classes, namely glycoside hydrolases, glycosyltransferases, polysaccharide lyases, carbohydrate esterases and redox enzymes with auxiliary activities (Lombard *et al.*, 2014). Several of the polysaccharide lyases, glycoside hydrolases and carbohydrate esterases are known as CWDEs that are used to degrade host cell walls. Typically plant pathogenic species contain higher numbers of CAZyme genes than saprophytic and animal pathogenic strains (Zhao *et al.*, 2013). Whereas obligate biotrophs typically lack extensive catalogs of CWDE genes and likely only use such enzymes for subtle manipulations of host cell walls such as at the cellular entrance sites for haustoria, necrotrophic fungi were often thought of as 'brute-force' pathogens that rely on large CWDE catalogs to macerate host cell walls and initiate colonization (Bolton *et al.*, 2006). These enzymes occur in multiple isoforms that not only differ in isoelectric point and molecular weight, but also in timing of their production and processing, offering especially broad host-range necrotrophs particular flexibility to penetrate and colonize their hosts. Besides colonization, these enzymes also liberate nutrients for the pathogen. For example, hydrolysis of pectin by fungal pectinases weakens the cell wall to enable penetration while also providing the fungus with important carbon sources for growth (Alghisi and Favaron, 1995). Indeed, strategies to limit pectin degradation were explored by generating transgenic wheat lines expressing pectin methyl esterase inhibitors, which exhibited altered pectin methyl esterification that resulted in reduced activity of pathogen pectic enzymes and reduced disease from hemibiotrophic pathogens *Fusarium graminearum* and *Bipolaris sorokiniana* (Volpi *et al.*, 2011). Similarly, wheat lines expressing genes encoding a xylanase inhibitor and

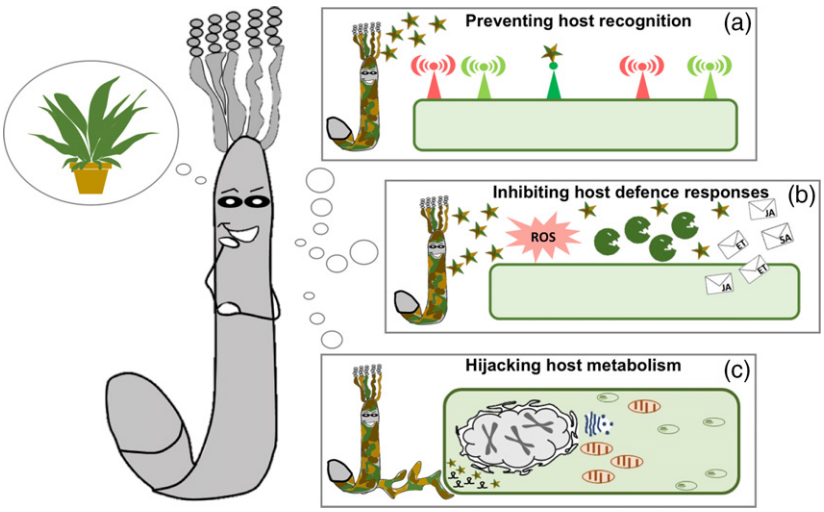

Figure 2. Illustration of fungal pathogen strategies to surmount host plants.
(a) Secretion of effectors that perturb recognition by plant immune receptors.
(b) Secretion of effectors that subvert plant defence responses that are induced upon pathogen detection.
(c) Delivery of various types of molecules to hijack host metabolism.

polygalacturonase-inhibiting protein exhibited increased resistance to Fusarium head blight (Tundo *et al.*, 2016). However, *F. graminearum* single-gene deletion mutants for polygalacturonase or xylanase resulted in minor effects on virulence, while double-gene mutants were significantly reduced in virulence on soybean and wheat plants, highlighting the synergism between CWDEs (Paccanaro *et al.*, 2017).

Besides plant CWDEs, fungi secrete CWDEs to modulate their own cell walls and accommodate morphological changes. It was recently proposed that such activity facilitates pathogenesis of plants by enabling host colonization. A glycosyltransferase enzyme from the hemibiotrophic wheat pathogen *Zymoseptoria tritici* was reported to enable hyphal growth on solid surfaces that is essential for fungal disease of wheat plants (King *et al.*, 2017). Homologues of this particular enzyme are widespread in fungi, and mutants in the taxonomically unrelated *F. graminearum* were similarly impaired in hyphal growth and pathogenicity (King *et al.*, 2017).

Fungal strategies preventing plant recognition

Plants evolved a plethora of plasma membrane-localized immune receptors for surveillance of the extracellular space for pathogen(-induced) ligands (Boller and Felix, 2009; Macho and Zipfel, 2014; Couto and Zipfel, 2016). The perception of these ligands is relayed into downstream signalling events that lead to the activation of plant defences (Bolton, 2009; Couto and Zipfel, 2016). Structural components of the fungal cell wall, such as glucans and chitin, are typically recognized as pathogen ligands by plant receptors (Felix *et al.*, 1993; Shibuya *et al.*, 1993; Cosio *et al.*, 1996; Cote *et al.*, 2000). As part of their defence system, plants secrete glucanases and chitinases to compromise the integrity of fungal cell walls and release oligomeric fragments that can act as ligands for extracellular immune receptors (Sanchez-Vallet *et al.*, 2015). Fungi have evolved several strategies to overcome host immune responses that involve fungal cell walls, including alterations in cell wall compositions and the secretion of effectors to protect cell walls or perturb recognition of cell wall components (Rovenich *et al.*, 2014; Sanchez-Vallet *et al.*, 2015).

Magnaporthe oryzae is a hemibiotrophic fungal pathogen and causal agent of rice blast disease (Dean *et al.*, 2005). During infection, *M. oryzae* responds to the epidermal wax component 1,16-hexadecanediol by accumulating α-1,3-glucans at the surface of the cell wall, resulting in inhibition of chitin degradation by plant chitinases (Fujikawa *et al.*, 2012). Accordingly, mutants that are unable to accumulate α-1,3-glucans at the fungal cell surface trigger rapid activation of host defences (Fujikawa *et al.*, 2012). A similar strategy has been reported for the maize pathogen *Colletotrichum graminicola* that modifies the β-glucan composition of its biotrophic hyphae, as the content of β-1,3- and β-1,6-glucans is significantly reduced when compared with appressoria and necrotrophic hyphae (El Gueddari *et al.*, 2002; Oliveira-Garcia and Deising, 2013, 2016). Hence, *C. graminicola* strains that overexpress a β-1,3-glucan synthase in their biotrophic hyphae induce stronger host defence responses and display reduced virulence (Oliveira-Garcia and Deising, 2013). However, *C. graminicola* strains that are unable to produce β-1,6-glucans are defective in appressorium formation and thus non-pathogenic (Oliveira-Garcia and Deising, 2016).

Modification of cell walls is not the only strategy employed by fungal pathogens to prevent plant recognition. For instance, the tomato leaf mould fungus *Cladosporium fulvum* secretes the carbohydrate-binding effector protein Ecp6 that suppresses chitin-triggered host immunity. The chitin-binding capacity of Ecp6 is mediated by three LysMs (de Jonge *et al.*, 2010; Sanchez-Vallet *et al.*,

2013) that occur in proteins of a wide range of organisms to confer the ability to bind various types of polysaccharides, including peptidoglycan and chitin, through a conserved βααβ-fold (Buist *et al.*, 2008). Interestingly, two out of the three LysM domains of Ecp6 cooperate to form a groove that binds chitin fragments with ultra-high (pM) affinity that allows to outcompete host receptors for chitin binding (Sanchez-Vallet *et al.*, 2013). Besides Ecp6, *C. fulvum* also secretes the chitin-binding effector molecule Avr4 during host colonization. As opposed to LysMs, Avr4 binds chitin through an invertebrate chitin-binding module to protect the cell wall against hydrolysis by host enzymes (van den Burg *et al.*, 2006; van Esse *et al.*, 2007). In contrast to Avr4 homologues that only occur in a limited set of fungi that are closely related to *C. fulvum* (Stergiopoulos *et al.*, 2010), LysM effector proteins occur in a wide variety of fungi (de Jonge and Thomma, 2009), and have been shown to suppress chitin-triggered immunity on various plant hosts such as for *Z. tritici* on wheat (Marshall *et al.*, 2011), for *M. oryzae* on rice (Mentlak *et al.*, 2012), for *Colletotrichum higginsianum* on Arabidopsis (Takahara *et al.*, 2016), and for *Verticillium dahliae* on tomato (Kombrink *et al.*, 2017).

Whereas chitin perception in plants is relatively well understood (Rovenich *et al.*, 2016), β-glucan perception and signalling mechanisms remain poorly characterized (Fesel and Zuccaro, 2016). The root endophyte *Piriformospora indica* secretes the β-glucan-binding lectin effector FGB1 that suppresses β-glucan-triggered host immunity (Wawra *et al.*, 2016). Prevention of β-glucan detection by the plant seems important for successful fungal infection as overexpression of the *P. indica* FGB1 homologue in *Ustilago maydis* was shown to lead to an increase in virulence. Interestingly, FGB1 homologues are widespread in fungi (Wawra *et al.*, 2016).

A further strategy to protect fungal cell walls and prevent detection of cell wall components is through the secretion of proteases that affect hydrolytic host enzymes (Albersheim and Valent, 1974). Fungal chitinase-modifying proteins (CMPs) have been reported in several maize pathogens, including *Bipolaris zeicola* (Naumann *et al.*, 2009), *Stenocarpella maydis* (Naumann and Wicklow, 2010) and *Fusarium verticilloides* (Naumann *et al.*, 2011). Similarly, *Fusarium oxysporum* f. sp. *lycopersici*, *V. dahliae* and *Botrytis cinerea* were found to secrete CMPs that can degrade extracellular tomato chitinases (Jashni *et al.*, 2015a).

Fungal strategies for inhibiting host defence responses

Pathogen recognition by plants results in a panoply of defence responses to hamper pathogen invasion. These responses comprise swift ion fluxes, pH changes, production of ROS, but also the production of local and systemic signalling molecules and antimicrobial compounds. Various mechanisms are employed by fungal pathogens to subvert such responses.

Subverting ROS damage. Reactive oxygen species production is mostly due to the activity of membrane-bound NADPH-oxidases and cell-wall-associated peroxidases (POX; Bolwell *et al.*, 2002; Sasaki *et al.*, 2004; Bindschedler *et al.*, 2006). While relatively low concentrations of ROS have been reported to act as defence signalling molecules (Lamb and Dixon, 1997; Orozco-Cardenas *et al.*, 2001; Qi *et al.*, 2017), high concentrations of ROS are extremely harmful to cells as they have been shown to cause oxidative damage (Levine *et al.*, 1994; Wu *et al.*, 1997). The apoplastic effector Pep1 of the biotrophic maize pathogen *U. maydis* accumulates at sites where biotrophic hyphae move from cell to cell in maize tissue to inhibit the oxidative burst through inhibition of POX12, a type-III class heme-peroxidase that is highly induced after *U. maydis* penetration (Doehlemann *et al.*, 2009; Hemetsberger *et al.*, 2012). Pep1 only causes partial inhibition of the maize apoplastic peroxidase activity, suggesting that not all peroxidase-producing enzymes in the maize apoplast are targeted by Pep1 (Hemetsberger *et al.*, 2012).

Manipulating tissue pH. Many fungal pathogens induce a pH shift in the host tissue surrounding the infection site (Prusky and Yakoby, 2003). For instance, *Sclerotinia sclerotiorum* causes acidification of the infection area through the production of oxalic acid, leading to rapid death of host tissues (Bolton *et al.*, 2006). However, other pathogens induce alkalinization of host tissue (Prusky *et al.*, 2001; Masachis *et al.*, 2016). During host colonization, the vascular wilt pathogen *F. oxysporum* causes an increase of the extracellular pH from about 5 to 7 through the secretion of a peptide with homology to plant rapid alkalinizing factors (RALFs; Murphy and De Smet, 2014; Masachis *et al.*, 2016). Interestingly, *F. oxysporum* strains that are no longer able to produce this peptide trigger enhanced host defence, indicating a role in suppression of host immunity. Although this role in virulence has been challenged (Thynne *et al.*, 2017), RALF-encoding genes can be found in many fungal pathogens, suggesting a universal mechanism to alkalinize infection sites to suppress host immunity (Masachis *et al.*, 2016; Thynne *et al.*, 2017).

Inhibition of host proteases. Many of the molecules that fungal pathogens secrete in order to establish the parasitic interaction with their hosts are of a proteinaceous nature, and hence plants secrete proteases to undermine this pathogen strategy (van der Hoorn, 2008; Jashni *et al.*, 2015b). The apoplast of tomato and Arabidopsis contains various proteases that contribute to host defence (Shabab *et al.*, 2008; van Esse *et al.*, 2008). Among these, the tomato apoplast contains the extracellular cysteine

protease Rcr3 that plays a central role in resistance mediated by the Cf-2 immune receptor of tomato and that is activated by the *C. fulvum* effector Avr2 (Kruger *et al.*, 2002). The Avr2 effector inhibits the activity of Rcr3, likely causing a conformational change in the Rcr3 structure that is recognized by Cf-2 (Kruger *et al.*, 2002; Rooney *et al.*, 2005). Besides Rcr3, Avr2 inhibits various other host proteases that are required for pathogen defence (van Esse *et al.*, 2008). Other fungal pathogens also produce protease effectors to inhibit host proteases, such as the *U. maydis* Pit2 effector (Doehlemann *et al.*, 2011; Mueller *et al.*, 2013).

Subverting hormone signalling. Plant growth and their responses to environmental cues, including pathogens, are largely governed by phytohormones. Typically, salicylic acid (SA) signalling governs resistance against biotrophic pathogens, whereas a combination of jasmonic acid (JA) and ethylene (ET) signalling activates resistance against necrotrophic pathogens (Thomma *et al.*, 1998, 2001; Glazebrook, 2005). To a large extent, these signalling pathways act antagonistically and their balance needs to be governed carefully. Thus, it is not surprising that pathogens evolved various strategies to affect phytohormone signalling. For instance, *U. maydis* secretes the chorismate mutase Cmu1 into host cells to perturb SA production by affecting the production of its precursor (Djamei *et al.*, 2011). Likely, Cmu1 acts in combination with the maize chorismate mutase Cm1 to increase the flow of chorismate from the plastid to the cytosol to diminish the available substrate for SA biosynthesis in plastids in turn (Djamei *et al.*, 2011). Furthermore, *U. maydis* produces Shy1, a salicylate hydroxylase that degrades SA during host invasion (Rabe *et al.*, 2013). Together these results suggest that perturbation of SA-mediated immunity is crucial for *U. maydis* colonization. Chorismate mutases have been identified in many eukaryotic plant pathogens pointing towards a common strategy for host manipulation. Similar to *U. maydis*, also *V. dahliae* has been proposed to target SA biosynthesis by secreting effectors with isochorismatase activity to hydrolyse isochorismate (Liu *et al.*, 2014). Besides targeting SA signalling, fungal effectors that target JA signalling or ET signalling have been described as well (Kloppholz *et al.*, 2011; Plett *et al.*, 2014). For instance, the beneficial fungus *Laccaria bicolor* produces the Mycorrhiza-induced small secreted protein-7 (MiSSP7) during the interaction with its host *Populus trichocarpa* (Plett *et al.*, 2014). Intriguingly, MiSSP7 interacts with the plant JASMONATE ZIM-DOMAIN (JAZ)-6 protein to provoke blockage of the expression of JA-inducible genes in the host to promote fungal colonization (Plett *et al.*, 2014).

Besides the capacity to manipulate hormone balances in plant tissues, particular fungi appear to have the ability to produce hormone-mimicking compounds to promote host colonization (Reineke *et al.*, 2008; Yin *et al.*, 2014; Chanclud and Morel, 2016; Chanclud *et al.*, 2016). For instance, *Fusarium pseudograminearum* produces cytokinin-like molecules that activate plant cytokinin signalling to reprogramme the host (Sorensen *et al.*, 2017).

The molecules that do the job: fungal effectors

Typically, fungal effectors are described as small secreted, cysteine-rich proteins that are produced during host invasion (Stergiopoulos and de Wit, 2009). These fungal effectors can be divided into two types based on their extra- or intracellular localization in the host. Yet, how cytoplasmic effectors are translocated into host cells remains poorly understood (Kale and Tyler, 2011; Ribot *et al.*, 2013; Petre and Kamoun, 2014). Nevertheless, two distinct secretion systems to target effectors have been described for *M. oryzae*. Cytoplasmic effectors accumulate in a so-called biotrophic interfacial complex, a plant membrane-rich structure associated with invasive hyphae that involves exocyst and t-SNARE components (Khang *et al.*, 2010; Giraldo *et al.*, 2013). By contrast, apoplastic effectors are secreted from invasive hyphae via conventional secretion. In addition to proteinaceous effector molecules, other types of molecules are secreted by fungi with the aim to establish the parasitic relationship that therefore qualify to be labelled as effectors just as well.

Secondary metabolites (SMs). Secondary metabolites are small bioactive molecules that often play crucial roles in the establishment of specific ecological niches but, unlike primary metabolites, are not essential for fungal growth, development or reproduction. While fungal SMs are often known and valued for their anti-microbial activities, many fungi employ SMs to promote virulence. Traditionally SMs involved with virulence are classified as either host-specific toxins (HSTs; discussed below), because they have specific targets in the host, or non-HSTs that typically do not have a specific host target and are generally toxic to a wide range of organisms including the host instead (Wolpert *et al.*, 2002). Perylenequinones, for example, are a family of photosensitizing SMs for which the mode of action is well studied. The most prominent member of the family is cercosporin. This light-activated toxin is produced by most *Cercospora* spp. and has a very broad toxicity range to many organisms, including plants, animals, bacteria and most fungi. Due to its photosensitizing nature, cercosporin is able to absorb light energy and subsequently react with oxygen (Daub and Ehrenshaft, 2000). Products of this reaction are ROS that can cause protein and DNA damage and lipid peroxidation, and eventually lead to cell death of the host (Blokhina *et al.*, 2003; Birben *et al.*, 2012). As necrosis development lays the ground for fungal spore formation, it is speculated that cercosporin secretion might facilitate cell wall breaching to enable conidiophore and conidia production (Weltmeier *et al.*, 2011). The cercosporin biosynthesis

gene cluster was recently shown to be found widespread in the *Colletotrichum* genus, implicating the role of cercosporin as a virulence factor in an important group of fungal plant pathogens (de Jonge *et al.*, 2017).

HSTs. Host-selective toxins are known to induce necrotic host tissue reactions to promote host susceptibility (Wolpert *et al.*, 2002). The effectiveness of HSTs depends on whether a plant possesses a corresponding toxin target, which may also define the host range of the producing pathogen. For example, maize lines harboring Texas cytoplasm for male sterility (Tcms) display extreme sensitivity to T-toxin and PM-toxin secreted by *Cochliobolus heterostrophus* race T and *Mycosphaerella zeae-maydis*, respectively (Levings III *et al.*, 1995; Wolpert *et al.*, 2002; Tsuge *et al.*, 2013). Here, host susceptibility is conferred by a single plant gene *T-urf13* that encodes URF13, a mitochondrial membrane protein to which either toxin can directly bind. Binding triggers URF13 to experience a conformational change that in turn results in the formation of a pore in the mitochondrial membrane. The ability to produce T-toxin is relevant for fungal virulence, as *C. heterostrophus* race O, a natural T-toxin lacking race and Tox1^{-}-deficient mutants of race T show reduced virulence on Tcms-carrying maize (Yang *et al.*, 1994). Similarly, PM-toxin-deficient Tox^{-} mutants of *M. zeae-maydis* lost the ability to infect Tcms maize (Yun *et al.*, 1998). Besides mitochondria, HSTs are also reported to target enzymes or other plant cell organelles like plasma membrane, chloroplast, endoplasmatic reticulum, nucleus, vacuole and Golgi bodies, with the objective to suppress host defence responses and/or induce host cell death (Meena *et al.*, 2017).

Another HST toxin is victorin, a family of related, cyclized pentapeptides (Wolpert *et al.*, 1985, 1986) secreted by the necrotrophic fungus *Cochliobolus victoriae* that causes Victoria blight on susceptible oats (Meehan and Murphy, 1947). Fungal pathogenicity is solely attributed to the ability to produce victorin, as victorin-deficient mutants are entirely non-pathogenic (Scheffer *et al.*, 1967). While susceptibility of oats can be traced back to one dominant gene called *Vb* (Welsh *et al.*, 1954), it was later found that a single, dominant gene, called Locus Orchestrating Victorin Effects1 (LOV1), provides victorin susceptibility in Arabidopsis plants (Gilbert and Wolpert, 2013). Interestingly, only oat lines carrying *Pc2*, a resistance gene against crown rust, are susceptible to victorin-producing *C. victoriae* isolates (Litzenberger, 1948; Welsh *et al.*, 1954). As studies to create plants resistant to both Victoria blight and crown rust were unsuccessful, it was suggested that *Vb* and *Pc2* are the same gene conferring susceptibility and resistance, respectively (Litzenberger, 1948; Mayama *et al.*, 1995). Further evidence for this hypothesis was provided by the discovery that victorin perception triggers a defence response in susceptible oats and Arabidopsis (Wolpert *et al.*, 2002; Gilbert and Wolpert, 2013), hinting that *C. victoriae* hijacks the classic gene-for-gene interaction needed to provide resistance against crown rust and utilizes victorin to elicit host cell death via the same defence mechanism to suit its necrotrophic lifestyle.

The necrotrophic fungus *Parastagonospora nodorum* (formerly *Stagonospora nodorum*) is the causal agent of the Septoria nodorum blotch (SNB) disease on wheat (King *et al.*, 1983; Oliver *et al.*, 2012). Besides the ability to produce CWDEs and non-specific toxins, *P. nodorum* has been characterized for its ability to produce a wide range of HSTs (also called necrotrophic effectors) that result in different levels of susceptibility depending on the wheat cultivar (Keller *et al.*, 1994; Wicki *et al.*, 1999a,b; Friesen and Faris, 2010). So far, a total of nine interactions between necrotrophic effectors of *P. nodorum* and corresponding wheat susceptibility genes have been found (Liu *et al.*, 2004a,b, 2006; Friesen *et al.*, 2006, 2007, 2008, 2009, 2012; Abeysekara *et al.*, 2009, 2012; Chu *et al.*, 2010; Zhang *et al.*, 2011b; Gao *et al.*, 2015; Shi *et al.*, 2015). Furthermore, it was reported that homologues of the necrotrophic *P. nodorum* effector gene *ToxA* have been acquired via horizontal gene transfer and interspecific hybridization by the wheat pathogens *Pyrenophora tritici-repentis*, *Phaeosphaeria avenaria triti* and *B. sorokiniana* (McDonald *et al.*, 2017). So far, two host targets *Snn1* and *Tsn1*, of *P. nodorum* necrotrophic effectors ToxA and Tox1, respectively, have been cloned (Faris *et al.*, 2010; Shi *et al.*, 2016). While *Tsn1* resembles a plant resistance gene structure as it harbors a serine/threonine protein kinase, a nucleotide binding and leucine-rich repeat domains (Faris *et al.*, 2010), *Snn1* is a wall-associated kinase with a predicted transmembrane domain (Shi *et al.*, 2016). However, in both cases interaction with a corresponding necrotrophic effector leads to a so-called necrotrophic effector-triggered susceptibility (Friesen *et al.*, 2007; Faris *et al.*, 2010; Liu *et al.*, 2012; Shi *et al.*, 2016) in opposition to the conventional effector-trigger immunity (ETI) observed in most of the biotrophic interactions. Taken together, these studies suggest that some necrotrophic fungal pathogens use effectors to subvert the host resistance mechanism for their own benefit (Wolpert *et al.*, 2002; Liu *et al.*, 2012, 2015).

Non-typical effectors: sRNAs. Small RNAs (sRNA) induce gene silencing by binding to Argonaute (AGO) proteins and directing the RNA-induced silencing complex to genes with complementary sequences (Castel and Martienssen, 2013). As regulatory molecules, sRNAs are involved in a wide range of biological processes, such as organ morphogenesis, genome modification, and adaptive responses to abiotic and biotic stresses (Carrington and Ambros, 2003; Ruiz-Ferrer and Voinnet, 2009; Katiyar-Agarwal and Jin, 2010). Both animals and plants have been reported to

exchange sRNAs with parasites, pathogens or symbiotic organisms in cross-kingdom sRNAs transfer (Wang *et al.*, 2016). It is generally assumed that sRNAs from plants are integral components of plant responses to adverse environmental conditions, including host–microbial interactions (Katiyar-Agarwal and Jin, 2010; Zhang *et al.*, 2011a). While host sRNAs play important roles in pathogen resistance, pathogens also encode sRNAs to manipulate host defence responses and mediate virulence (Weiberg *et al.*, 2013; Chaloner *et al.*, 2016; Wang *et al.*, 2016). The necrotrophic fungus *B. cinerea* infects almost all vegetable and fruit crops, causing major losses worldwide. Recently, it has been reported that some *B. cinerea* sRNAs (Bc-sRNAs) can silence Arabidopsis and tomato genes involved in immunity (Weiberg *et al.*, 2013). The produced Bc-sRNAs hijack the host RNA interference (RNAi) machinery by binding to Arabidopsis AGO1. Furthermore, Bc-sRNAs silence host target immunity genes in both Arabidopsis and tomato plants during fungal infection (Weiberg *et al.*, 2013). Cross-kingdom RNAi to suppress host immunity genes by hijacking host AGO1 has also been reported for *V. dahliae* (Wang *et al.*, 2016). Arabidopsis ago1-27 mutants were less susceptible to the infection with *V. dahliae* than wild-type plants in both soil and root culture conditions (Wang *et al.*, 2016). These results indicate that fungal pathogens and hosts utilize cross-kingdom RNAi to manipulate their interactions to their own benefit.

Evolution of pathogen virulence

As effectors are pathogen molecules that are crucial for establishing the parasitic symbiosis, hosts continuously evolve to intercept pathogen effectors or their activities with their immune receptor repertoire to halt pathogen ingress (Cook *et al.*, 2015). To avoid or overcome such recognition, pathogens need to be able to swiftly purge or modify effectors that are intercepted by host immune systems, or evolve novel effectors to suppress the reinstated immune response, leading to an everlasting co-evolution between pathogen and host (Jones and Dangl, 2006; Cook *et al.*, 2015). Based on genomics of plant pathogenic species, it has been proposed that many pathogens possess a bipartite genome architecture where effector genes cluster in repeat-rich dynamic compartments, a phenomenon that has been coined a 'two-speed' genome (Croll and McDonald, 2012; Raffaele and Kamoun, 2012). These regions are typically repeat-rich, sometimes with active transposable elements (TEs), and often display increased structural polymorphism, increased point mutagenesis and positive selection (Raffaele *et al.*, 2010; Rouxel *et al.*, 2011; de Jonge *et al.*, 2013; Dong *et al.*, 2015; Faino *et al.*, 2016; Möller and Stukenbrock, 2017). TEs are likely to contribute to pathogen adaptation by facilitating the swift evolution of effector catalogues by establishing genetic variability (Faino *et al.*, 2016; Bao *et al.*, 2017), yet the underlying mechanisms remain largely unknown (Seidl and Thomma, 2017). However, genomic analysis in *V. dahliae* revealed active and passive contributions of TEs, through TE activity, and through acting as substrate for homology-based double-strand repair pathways, respectively (Faino *et al.*, 2016).

To control the spread and activity of TEs, TE-rich genomic regions are often highly condensed in heterochromatin, which is directed by DNA methylation. As effector genes and other virulence-related genes, such as toxin biosynthesis genes, often reside in TE-rich regions, TEs can impact the expression of these genes (Connolly *et al.*, 2013; Chujo and Scott, 2014; Soyer *et al.*, 2014). Consequently, specific and differential methylation may be associated with adaptive evolution of two-speed pathogen genomes (Seidl *et al.*, 2016; Chen *et al.*, 2017; Seidl and Thomma, 2017). Thus, TEs drive genome and transcriptome variability that, in turn, impacts pathogen adaptation (Seidl and Thomma, 2017).

CONCLUSION

While all plant pathogenic fungi come across common plant defence mechanisms during host colonization, they employ different strategies to bypass these. As the ongoing co-evolution with their hosts prompts pathogens to appropriately respond to modifications in host immunity in a timely manner, fungi need to continuously adapt their repertoire of virulence strategies to keep their parasitic relationships ongoing. A deep understanding of the molecular mechanisms underlying these virulence strategies and host–pathogen interactions will result in the identification of precise virulence targets in the host plant. Such knowledge is paramount to improve current crop protection strategies or to design novel measures for disease control.

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