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CHAPTER 7

HOST SPECIFICITY IN *PHYTOPHTHORA*: A CONUNDRUM OR A KEY FOR CONTROL?

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ABSTRACT

The Oomycete, *phytophthora* causes devastating diseases in almost all ecological niches. It is a hemibiotroph, and has a 'two speed genome' which underpins a rapid evolution of the vast repertoire of virulence (effector) genes present. This brings about an ability to rapidly co-evolve and thereby adapt to resistant hosts has making it one of the most devastating of phytopathogens. Added to that is its variation in host ranges from a single host to hundreds of genera for certain species. Each having different host–pathosystem interaction and dynamics making complete control apparently impossible. Yet there seems to be a method in this diversity, which can be exploited. The effectors are often the key in determining host specificity and their interaction are essential for successful infection or vice versa. An understanding of how these effectors interact and function is perhaps a key out of this conundrum as they then can be targeted. This article discusses the above aspects.

7.1 INTRODUCTION

The sixth kingdom oomycetes, includes some of the most devastating pathogens on both cultivated crops and wild plants. Within them, *phytophthora* is a genus of plant pathogenic filamentous oomycetes containing more than one hundred species. Virtually all of them are plant pathogens causing many well-known and important plant diseases worldwide, such as potato late blight, sudden oak death (SOD), and forest dieback caused by *phytophthora infestans*, *phytophthora ramorum*, and *phytophthora cinnamomi*, respectively. Notwithstanding the fact that it causes numerous other diseases in almost all ecological niches (Erwin & Ribeiro, 1996, Lamour, 2013, Guha Roy & Grunwald, 2014). In the genus *phytophthora* some closely related species have a broad host range, while others are very host specific. Pathogenicity and host adaptation are, therefore, essential traits to understand its biology and to come up with durable, efficient management. However, this becomes a challenge when one considers that most of species are pathogenic, have different host–pathogen dynamics, dearth of comparative genomics data of infection in different hosts and extremely broad host range of about 255 plant genera from 90 families (Cline et al., 2008) in some species like *p. nicotianae*. This is compounded when interspecific hybridization which is becoming increasingly evident as a common event in *phytophthora* evolution extends the host range further and yet the consequences for its ecological fitness and distribution are not well understood. (Bertier et al., 2013).

Yet, perhaps the key to control lies in this very seemingly host complexity which can be unraveled with comparative proteomics and genomics of host–pathogen interaction to dissect the basis for difference in virulence strategies of the strains against the host range. The key here being the nature, differences and timing of the effectors secreted by the *phytophthora* spp. *vis-a-vis* it's hosts. Host specificity of *phytophthora* spp. is presumably based on differences in early infection events namely that of effector classes. The differential pathogenic response against a broad range of hosts is the key to strategizing control measures for the pathogen. Such responses to a large extent depend on the diversity, spatial and temporal regulation of effector classes, differences in early interaction events and on selection pressure of the pathogen populations which determine the virulence potential. Identifying effector elements responsible for interfering with pathogen-associated molecular patterns (PAMP) and effector triggered immunity (ETI) pathway and bringing about differential specificity in its host range will be the key to control as these can then be targeted.

7.2 THE CONUNDRUM

The development of modern agriculture has been shaped by oomycete plant pathogens. Three major epidemics spread over Europe in the middle nineteenth century. Potato, citrus, and grapevine productions were devastated by *phytophthora infestans*, a complex of *p. citrophthora* and *p. nicotianae*, and *plasmopara viticola*, respectively, (Erwin & Ribeiro, 1996) and recently that of forest tree pathogen, *phytophthora ramorum*, the SOD causal agent (Werres et al., 2001). The potential risk due to this introduced pathogen contributed to the release of its complete genome only 5 years after its formal description (Tyler et al., 2006), and *p. ramorum* is now considered as one of the most devastating oomycetes (Kamoun et al., 2015). The human and economical losses were so important that they definitively impacted human history. This leads to the emergence of plant pathology as a formal science, the exploitation of empiric observations to favor the use of resistant plants (Laviola et al., 1990), and to elaborate preparations directed against pathogens, such as the Bordeaux mixture (Rivière et al., 2011). And accordingly, breeding for resistant cultivars and chemical control by fungicides became the cornerstones of nearly all crop protection strategies for more than a century.

The initial studies of twentieth century lead to the description initially of ~60 *phytophthora* species which greatly differed in their biology,

reproductive strategy and pathogenicity (Erwin & Ribeiro, 1996). Additionally, now more than 70 new species have been identified after 2000, and tens of provisional putative new species are awaiting a formal description in different laboratories around the world (Martin et al., 2014; Guha Roy & Grunwald, 2014). Considering that there are 200–600 extant *phytophthora* species (Brasier, 2009), a large number of species, therefore, remain to be discovered.

Notwithstanding these facts, the ~4,400 host–pathogen associations identified with *phytophthora* spp. worldwide are also rapidly evolving (Scott et al., 2013). These changes concern not only the newly identified species, but also some of the earliest *phytophthora* species to be described, like *p. infestans* (Cooke et al., 2012) or *p. nicotianae* (Panabières, et al., 2016).

7.3 QUESTIONS THAT NEED TO BE ANSWERED

So the questions that need to be answered are; do host-govern specificity in these different *phytophthora*-phytopathosystems or are there different characteristics and mechanisms for selective pathogenesis within *phytophthora* of different host origin? Are these mechanisms different or have they evolved from the basic repertoire and have differentiated due to different selection pressures including climate changes? If so, then, did host specific *phytophthora* spp. evolve from broad host range species? Did host-specific *phytophthora* spp. co-evolve with their host plants or did sympatric speciation occur at a much later stage in the evolution of the pathogen? The *phytophthora* genus provides a fascinating range in complexities of these host–pathogen associations. Host ranges of *phytophthora* species can vary from one extreme of being very diverse to that of a single host. Some species, like*p. cinnamomi* and *p. nicotianae* may attack hundreds of plants with *p. nicotianae* having the broadest range while others, like*p. infestans* have a narrow host range or *p. sojae,* which infects a single host. Host ranges of new invasive forest (*p. ramorum*) or other *phytophthora* species are being determined but the range continues to expand with passage of time (Grünwald et al., 2008, Schwingle & Blanchette, 2008). Also, molecular validation and renaming of species are now often increasingly changing host boundaries for each species (e.g., *p. palmivora* MF4 [= *p. capsici*]–*p. tropicalis*). Most crops of agricultural importance and natural ecosystems were shown to be preferentially associated to a *phytophthora* species, like potato and tomato (*p. infestans*), soybean (*p. sojae*), tobacco (*p. nicotianae*), or Australian jarrah trees (*p. cinnamomi*). Yet, some plants were hosts of several *phytophthora* species. In these cases,

a given species may be prominent and induce more severe symptoms than another, leading to the definition of primary and secondary pathogens.

7.4 HOST–PATHOGEN INTERACTIONS AND HOST SPECIFICITY

This outcome of host–pathogen interactions is determined by a fine-tuned molecular interplay between the two partners. Some species are soilborne (*p. sojae*, *p. nicotianae*) other are foliar (*p. infestans*) and understandably their mechanisms for host infection will differ to take into account this fact. The infection cycle of *phytophthora* spp. is initiated by the attraction of swimming zoospores to plant roots. In most cases, penetration of the root epidermis is mediated by appressorium-like structures (Tyler, 2007; Attard et al., 2008), but the direct penetration of hyphae between root cells has been reported for*p. sojae* (Enkerli et al., 1997). Following penetration, bulbous hyphae invade the roots intercellularly (Benhamou & Co ˆte ´, 1992; Widmer et al., 1998; Le Berre et al., 2008). During the interaction between soybean and*p. sojae*, this stage of infection involves a short, difficult-to-observe biotrophic phase (Hanchey & Wheeler, 1971) that seems to be associated with the differentiation of specialized feeding structures, called haustoria (Enkerli et al., 1997; Perfect & Green, 2001; Tyler, 2007).

However, differences also exist between those having similar mode of dissemination. *p. nicotianae* zoospores do not have plant species-specific root preferences in contrast to *p. sojae* zoospores which are attracted specifically to roots exuding the isoflavones diadzein and genistein. (Attard et al., 2008). But this specific chemotaxis toward host isoflavones is of limited importance in *phytophthora sojae* and *phytophthora vignae*, while, specific chemotaxis of *phytophthora pisi* and *phytophthora niederhauserii* indicated an adaptation to their pathogenicity on the host and lack of pathogenicity on non-host plants (Hosseini et al., 2014). Differences exist even between colonization of *a. thaliana* roots by *p. nicotianae* and *p. capsici* both of which are successfully and are able to complete their disease cycle in this *a. thaliana* host. The two oomycetes caused similar symptoms on the plants, but symptoms develop later following the infection in case of *p. nicotianae* than in *p. capsici*. Differential responses have also been seen in activation of signaling pathways in response to infection in leaves and roots. In experiments with *a. thaliana* it has been seen that the salicylate- and jasmonate-dependent signaling pathways are concertedly activated when*p. nicotianae* penetrates the roots, but are down-regulated during invasive growth, when ethylene (ET)-mediated signaling predominates. Defense responses in *a.*

thaliana roots are triggered immediately on contact with *p. nicotianae* but the pattern of early defense mechanism activation differs between roots and leaves (Attard et al., 2010). During leaf infections, switches from biotrophy to necrotrophy are frequently accompanied by a shift of plant defenses from salicylic acid (SA)- to jasmonic acid (JA)-mediated responses and is in contrast with the reported antagonistic action of the signaling pathways involving SA and JA/ET in leaves (Glazebrook, 2005). Similarly, it was found that beech root responses to *phytophthora citrocola* differed from leaf responses, and showed that most of the genes activated in roots had no known function or no matches with database sequences for genes activated in aerial parts of plants Schlink (2009).

7.5 HOST ADAPTATION/HOST SPECIFICITY RELATED TO POPULATION BIOLOGY AND EVOLUTION OF THE PATHOGEN

Host adaptation also has a population biology perspective. While host specificity at the genus/species or at the cultivar level allows to define the host range and physiological races of the pathogen, the quantitative assessment of the disease induced in susceptible hosts is a major, but completely different component of pathogenicity. Related to which is the extent of pathogenic variation present in "old" and "new" pathogen populations which was responsible for the loss on *hitherto* non hosts or marginal/resistant cultivars hosts. In addition, rapid shifts among pathogen populations may generate strains that overcome fungicides and/or resistant varieties, and thus challenge disease management programs.

Host specificity is not only of pathological, but also of evolutionary significance, because the possibility for infecting more than one host determines to a large extent the availability of "green bridges" during the pathogen's life cycle. These are critical in maximizing survival opportunities in species with very low saprophytic abilities, such as *p. infestans*, and probably condition the extent of gene flow between isolates (Andrivon et al., 2004). Host specificity may also have led to a speciation event as between *p. infestans* and *p. mirabilis*, two species giving rise to fertile hybrids (Goodwin & Fry, 1994), morphologically indistinguishable from one another (Galindo & Hohl, 1985), but with mutually exclusive host ranges. This separation of host ranges explains the reproductive isolation of *p. infestans* and *p. mirabilis* in nature. Other similar speciation patterns have also been described in South America (Adler et al., 2002) which involve sympatric wild and/or

cultivated hosts and which points to a selective advantage to host specialization in habitats where a number of potential hosts are present (Lapchin, 2002). As a result, current research (Lassiter et al., 2015) has proven that the *p. infestans* pathogen is closely related to four other *phytophthora* species in the 1c clade including *p. phaseoli*, *p. ipomoeae*, *p. mirabilis*, and *p. andina* all of which are important pathogens of other wild and domesticated hosts and that *p. andina* is an interspecific hybrid between *p. infestans* and an unknown *phytophthora* species. The formation of hybrids is perhaps the ultimate survival strategy: Reaching of new hosts through interspecific hybridizations as they would possess an unprecedented repertoire of virulence determinants inherited from both parents (Panabieries, 2015) and many examples of natural interspecific hybrids abound in this genus: *phytophthora* × *pelgrandis* from different hosts (Man In't Veld et al., 1998; Man in 'T Veld et al., 2012; Faedda et al., 2013; Szigethy et al., 2013); *p. alni* subsp. *uniformis* and *p. alni* subsp. *multiformis* (Ioos et al., 2006).

However, this general trend toward specialization (i.e., restriction of host range) is sometimes reverted, as shown by the discovery in the Netherlands of isolates overcoming the resistance of *solanum nigrum*, until then regarded as a non-host for *p. infestans* (Flier et al., 2003a). Another such example could perhaps be *phytophthora nicotianae* isolated from potato. *p. nicotianae* has been sporadically reported to cause foliar blight and tuber rot of potato over the past 75 years, but was generally considered of minor incidence (Taylor et al., 2015), but is now being increasingly reported as an important component of the tuber rot and foliar disease complex in US (Taylor et al., 2008), (Taylor et al., 2012). The concern here is that the *p. nicotianae* isolates recovered from potato are significantly more aggressive on this plant compared to *p. nicotianae* isolates recovered from other hosts (Taylor et al., 2012), suggesting potential host specialization and increasing of host range. This phenomenon leads one to recall the origins of *phytophthora* species attacking legumes in Australia (Irwin et al., 1997). It is becoming increasingly evident that interspecific hybridization is a common event in *phytophthora* evolution. Yet, the fundamental processes underlying interspecific hybridization and the consequences for its ecological fitness and distribution are not well understood. It has been hypothesized that interspecific hybridization and polyploidy are two linked phenomena in *phytophthora*, and that these processes might play an important and ongoing role in the evolution of this genus (Bertier et al., 2013).

7.6 THE KEY: GENOME STRUCTURE AND PATHOGENICITY FACTORS (EFFECTOR) SPECIALIZATION LEADING TO HOST SPECIFICITY/DIVERSIFICATION AND SPECIATION

As a rule, *phytophthora* diseases were more or less efficiently managed through cultural practices, fungicide applications, and the use of resistant varieties when available. In addition, rapid shifts among pathogen populations may generate strains that overcome fungicides and/or resistant varieties, and thus challenge disease management programs. The oomycetal world suffered extensive modifications while entering the twenty-first century both in terms of emergent species and advances in science, which resulted in resources, such as whole genome sequences of *phytophthora* species. The first *phytophthora* genomes, *p. ramorum* and *p. sojae*, became available in 2004, followed shortly by *p. infestans* in 2006 (Tyler et al., 2006; Haas et al., 2009) and *p. capsici* (Lamour et al., 2012) with the latest being *phytophthora fragariae* var. *fragariae* (Gao et al., 2015). These genome sequences of *phytophthora* will enable translational plant disease management and accelerate research (Grunwald, 2012) and have changed our understanding of host defenses and infection processes.

In general, the success of oomycetes as plant pathogens depend on their ability to suppress or evade host-defense responses and to gain nutrition and proliferate. During infection, oomycete pathogens secrete a variety of extracellular proteins such as cellulose binding elicitor lectin (CBEL) (Gaulin et al., 2006) and cell wall degrading enzymes that contribute to adhesion to the plant surface and plant cell wall degradation, respectively, and therefore to pathogenicity (Kamoun, 2006). In addition, *phytophthora* species secrete effector proteins to modulate biochemical, morphological, and physiological processes of their hosts. These proteins can be divided into two broad categories, apoplastic, and cytoplasmic effectors with different target sites in the plant. Apoplastic effectors accumulate in the plant intracellular space and include necrosis-inducing proteins (NIPs) (Qutob et al., 2002), elicitins that are small cysteine-rich proteins (Kamoun, 2006) and different enzyme inhibitors such as serine protease inhibitor (EPI) (Tian et al., 2005) and glucanase inhibitor (GIP) (Denance et al., 2013). Cytoplasmic effectors are translocated into the plant cytoplasm and include two expanded gene families in *phytophthora*, known as RXLR effectors (Birch et al., 2006) and Crinklers (CRNs) (Torto et al., 2003). The RXLR effectors share the conserved RXLR amino acid motif (arginine, any amino acid, leucine, arginine), the domain required for delivery inside plant cells, followed by diverse, rapidly evolving carboxy-terminal domains that are responsible for the virulence-related

function of the effectors (Birch et al., 2008). CRNs are NIPs that have a conserved FLAK motif for translocation, and are targeted to the host nucleus upon delivery (Schornack et al., 2010). Differences in gene family expansion and diversity, in particular dynamic repertoires of effector genes, are probably responsible for different traits among *phytophthora* species, such as altered host specificity. Interestingly, unlike the RXLR effectors, CRNs are present in the genome and transcriptome of all examined plant pathogenic oomycete species including *pythium ultimum*, *albugo candida*, and *a. euteiches* indicating that the CRNs form an ancient effector family that arose early in oomycete evolution (Schornack et al., 2010).

Genome structure analysis of these three *phytophthora* species revealed that the conserved genes are present in regions where gene density is high and repeat content is relatively low (the core genome), whereas non-conserved genes are located in regions with low gene density and high repeat content (the plastic genome). The core genome contains genes involved in cellular processes such as DNA replication, transcription and protein translation, whereas genes involved in plant infection, such as fast-evolving effectors, are predominantly located in the gene-sparse or plastic region, which is highly dynamic (Mollahossein, 2015). This probably plays a crucial part in the rapid adaptability of these pathogens to host plants and derives their evolutionary potential (Haas et al., 2009).

More than 1000 effectors described for *phytophthora* species have the potential to manipulate host metabolism (Vleeshouwers et al., 2006). Despite the broad range of compatible *phytophthora*–host interactions that cause diseases worldwide, the biological functions of elicitins as virulence factors during susceptible infections are barely discussed in literature. The molecular mechanism of elicitins, a conserved protein secreted by almost all *phytophthora* species, was deciphered and it was demonstrated that blocking elicitins caused loss of pathogen virulence. As a consequence, elicitins could be a target in plant–*phytophthora* interactions to prevent infection. Le Berre et al. (2008) demonstrated for the first time the importance of elicitins, particularly of α-plurivorin, for pathogen penetration and its involvement in plant-defense suppression. This is in concert with similar data showing that a strain of *p. cinnamomi* silenced for the β-cinnamomin gene, which is involved in β-cinnamomin elicitin synthesis, was unable to invade root tissue actively and cause disease symptoms (Horta et al., 2010). These results give strong evidence that α-plurivorin is directly involved in manipulation of plant defenses by a broad down-regulation of defense-related genes, independently of the signaling pathways. Furthermore, up-regulation of WRKY, PR1, and ACO after blocking α-plurivorin suggests that the α-plurivorin can

be also correlated with suppression of either PTI or ETI, therefore, acting as an effector triggering susceptibility (ETS).

Remarkably, the data of Le Berre et al. (2008) demonstrated that, even considering the presence of hundreds of effector genes in the *p. plurivora* genome, the blocking of α-plurivorin function compromises *p. plurivora* pathogenicity, thus suggesting its essential role for virulence. Because elicitins are highly conserved proteins (with high similarity (Yu et al., 1995) and are almost ubiquitously secreted by all *phytophthora* species (Takemoto et al., 2005), it will be of interest to investigate their role as virulence factors in other *phytophthora*-susceptible plant interactions. More importantly, the results found in this work open new perspectives toward the use of elicitins as specific targets for protecting plants against *phytophthora* infection. It opens a new horizon to the plant-pathology field, since one can disturb this complex system between plants and pathogens, giving advantage to the plants. Most of the plants can defend themselves against pathogens; however, successful pathogens secrete effectors to mock plant-recognition of infection, including *p. plurivora* (Schlink, 2010). Any disturbance of the mode of action of effectors could activate plant-defense responses. In fact, a very punctual disturbance of the system, such as blocking the acidic elicitin α-plurivorin of *p. plurivora* among hundreds of other effectors, resulted in loss of virulence and simultaneously activation of plant defense. Scientists have also figured out that silencing of one single effector can compromise pathogenicity. One example is given by Yu et al. (2012), who proved that silencing the RxLR effector Avh241, from among the about 627 RxLR in total (Tyler et al., 2006) resulted in loss of virulence of *p. sojae* to soybeans. These growing evidences led Kale (2012) to state that "effector blocking technologies could be developed and utilized in a variety of important crop species against a broad spectrum of plant pathogens."

More recently, Researchers at Oxford University and The Sainsbury Laboratory, Norwich, (Dong et al., 2014) looked in unprecedented detail at how *phytophthora infestans*, a pathogen that continues to blight potatoes and tomatoes today, evolved to target other plants. The study, used *phytophthora infestans* and sister species *phytophthora mirabilis*, (a pathogen that split from *p. infestans* around 1300 years ago) to target the *mirabilis jalapa* plant, commonly known as the four o'clock flower to show definitively for the first time that there is a direct molecular mechanism underpinning the change in host specialization allowing pathogens over time to switch from targeting one species to another through changes at the molecular level. They found that each pathogen species secretes specialized effectors to shut down the

defenses of their target hosts. When a plant becomes infected, proteases help plants to attack the invading pathogens and trigger immune responses. *p. infestans* secretes protease inhibitor EPIC effectors that disable proteases in potatoes and tomatoes. These are highly specialized to block specific proteases in the host plant, fitting like a key into a "lock." The effectors secreted by *p. infestans* are less effective against proteases in other plants such as the four o'clock, as they do not fit well into the "locks." The researchers found that *p. mirabilis* evolved effectors that disable the defenses of the four o'clock plant but are no longer effective against potatoes or tomatoes. The EPIC effectors secreted by *p. infestans* have evolved to fit the structure of potato proteases just as *p. mirabilis* has evolved effectors that fit four o'clock proteases. Amino acid polymorphisms in both the inhibitors and their target proteases underpin this biochemical specialization. These results link effector specialization to diversification and speciation of this plant pathogen. Thus, the host specialization that led to evolutionary divergence depending on reciprocal single–amino acid changes that tailor the pathogen effector to a specific host protease, which is being disabled. Thus, small changes can open the door for a pathogen to jump to another species of host and, itself, diversify into another species of pathogen.

Dr. Renier van der Hoorn, co-author of the study from Oxford University's Department of Plant Sciences says that "If we could breed plants with proteases that can detect these stealthy EPIC effectors, we could prevent them from 'sneaking in' and thus make more resistant plants. Within the next decade, we plan to exploit the specialized nature of these effectors to develop proteases that are resistant to their action or can even trap them and destroy the pathogen. Potato and tomato plants with such proteases would be resistant to the blight pathogens, and combined with other resistant traits could provide another 'wall' of defence against the pathogens."

Similarly, studies on the extremely broad host pathogen *p. parasitica*, which is phylogenetically related to *p. infestans*, and overlaps its host range, including potato (Taylor et al., 2008), therefore, are expected to advance our knowledge on mechanisms underlying general pathogenicity and those governing host specificity. Additionally, comparative analyses on these two species varying in genome size (83 Mb for *p. parasitica* versus 240 Mb for *p. infestans*) will help in the understanding of the evolution of pathogenicity and host range among *phytophthora* spp. Toward this end a through the sequencing of the genome of a cosmopolite isolate and the subsequent sequencing of isolates of diverse, narrow host range and geographical origins, the international "*phytophthora parasitica* genome initiative"

project is enabling the characterization of genes that determine host range. Currently, an in-depth analysis of 14 sequenced genomes of *p. nicotianae* has been completed along with the characterization of the repertoire of effector proteins. As a broad host range pathogen, *p. parasitica* provides a unique opportunity for intra- and inter-specific, comparative analyses, looking at the extent of these families, their organization, their role in plant recognition and infection, and their evolution among strains and species that display broad or restricted host ranges. The identification of conserved and accessory sets of effectors, as well as other pathogenicity genes, will give clues to evaluate the evolutionary pressure of exposure to different host-defense responses to the diversification of effectors and their role in adaptation to host plants. (Kamoun et al., 2015) which in turn will allow us to target the pathogen.

7.7 CONCLUSION

In conclusion, plants can be attacked by a vast range of pathogen classes, causing substantial agricultural losses. The mind boggling host range of some *phytophthora* species makes control difficult, but the time has come for a paradigm shift in our approach by targeting pathogen effectors as they are secreted during infection playing a key role in disease biology and hence can be targeted allowing a translational output. What makes this focus on effectors more important is that effector specialization leads to diversification and speciation of this plant pathogen. But at the same time effector-induced adaptation to new hosts is an understudied topic and more studies are needed to investigate how *phytophthora* effector proteins evolve the ability to specialize on new hosts.

KEYWORDS

- **pathogens**
- **comparative genomics**
- **effector**
- **molecular mechanism**
- **pathogenicity**

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