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REVIEW

Late blight in tomato: insights into the pathogenesis of the aggressive pathogen *Phytophthora infestans* and future research priorities

Purabi Mazumdar[1] · Pooja Singh[1] · Dharane Kethiravan[1] · Idd Ramathani[2] · N. Ramakrishnan[3]

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Abstract

Main conclusion **This review provides insights into the molecular interactions between *Phytophthora infestans* and tomato and highlights research gaps that need further attention.**

Abstract Late blight in tomato is caused by the oomycota hemibiotroph *Phytophthora infestans*, and this disease represents a global threat to tomato farming. The pathogen is cumbersome to control because of its fast-evolving nature, ability to overcome host resistance and inefficient natural resistance obtained from the available tomato germplasm. To achieve successful control over this pathogen, the molecular pathogenicity of *P. infestans* and key points of vulnerability in the host plant immune system must be understood. This review primarily focuses on efforts to better understand the molecular interaction between host pathogens from both perspectives, as well as the resistance genes, metabolomic changes, quantitative trait loci with potential for improvement in disease resistance and host genome manipulation via transgenic approaches, and it further identifies research gaps and provides suggestions for future research priorities.

Keywords Crinkler · Effector · Molecular pathogenesis · Plant immunity · RXLR · Fungus

Introduction

Tomato (*Solanum lycopersicum* Mill.) is a highly popular horticultural crop cultivated worldwide, although it is prone to several plant pathogens (Singh et al. 2017). *Phytophthora infestans* (Mont.) de Bary, the causal agent of late blight of tomato, is one of the most aggressive pathogens of tomato and causes crop loss (Nowicki et al. 2012). *P. infestans* is a member of the *Peronosporaceae* family of the phylum Oomycota, and it infects the entire plant, including the stems, leaves and fruits of tomato (Erwin and Ribeiro 1996). In 2007, the late blight epidemic episode in inner Mongolia, China, caused damage to approximately 638,900 tons of tomato production (Li 2008). In addition, this disease is also reported to cause continual annual losses of winter tomato production in Florida, which is a USD 464 million industry and produces 36% of the total fresh tomatoes of USA (Schultz et al. 2010).

The major symptom associated with late blight in tomato is the formation of small blackish/brown lesions on leaves, fruit and stems that progress to water-soaked chlorotic spots, which ultimately lead to necrosis in the entire plant (Fig. 1). *P. infestans* reproduces by both sexual and asexual means, but infection (Fig. 2) via sexual spores is relatively rare (Fry 2008). Asexual spores are dispersed via air and seed, while sexual spores are dispersed via soil (Seifu 2017). Aerial dispersion of the pathogen occurs via asexual spores known as sporangia, which is the primary mode of infection for *P. infestans* (Leesutthiphonchai et al. 2018). Sporangia are formed in sporangiophores that are dispersed by wind or water and facilitate the rapid dispersal of the pathogen (Aylor 2003). Sporangia settle on the leaf surface, and under favourable conditions (20–25 °C and available nutrients), sporangia germinate directly and cause infection, while under unfavourable conditions (lower temperature of

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✉ Purabi Mazumdar
purabi@um.edu.my

[1] Centre for Research in Biotechnology for Agriculture, University of Malaya, 50603 Kuala Lumpur, Malaysia

[2] National Crops Resources Research Institute, Gayaza Road Namulonge, 7084 Kampala, Uganda

[3] ECSE, School of Engineering, Monash University Malaysia, 47500 Bandar Sunway, Malaysia

Fig. 1 *Phytophthora infestans* infected tomato foliage and fruits exhibiting necrosis

10–15 °C and low nutrients), sporangia cleave their multinucleate cytoplasm and release 3–8 biflagellate mononucleate motile zoospores (Fry 2008; Grenville-Briggs et al. 2005). Motile zoospores rapidly encyst and produce a germ tube that invades the plant leaves and stems through stomata or develops an appressorium that invades the cuticle and epidermal cell wall (Kots et al. 2017). Following the invasion, intracellular hyphae of the pathogen ramify within the host cells (Fig. 2). *P. infestans* has a hemibiotrophic lifestyle, with an initial biotrophic infection phase that mainly relies on living host cells followed by a necrotrophic phase in which host cell death is induced (Botero et al. 2018).

In addition to aerial dispersion, dispersion via seeds is another concern. Often, transport of asymptomatic infected fruits can disperse infected seeds to new locations. Asymptomatic infected fruit dispersion was the factor underlying the late blight epidemic in tomato in the eastern United States (Leesutthiphonchai et al. 2018). Dispersion via soil mainly occurs by oospores, in which sexual spores are produced by the two known mating types, A1 and A2 (Judelson 2007). Oospores are more tolerant than sporangia and can easily survive adverse conditions in soil between growing seasons (Drenth et al. 1995).

Control of *P. infestans* mainly relies on chemical fungicide applications and resistance breeding (Poudel et al. 2020). However, *P. infestans* is difficult to manage because of its high adaptability to overcome the resistance of host plants (Fry 2008; Hass et al. 2009). Although few resistance genes have been identified in wild relatives of tomato (Van der Vossen et al. 2003; Pel et al. 2009; Zhang et al. 2013), several of the resistance genes have been overcome by different strains of *P. infestans* (Vleeshouwers et al. 2011). The ability of the pathogen to overcome the resistance was

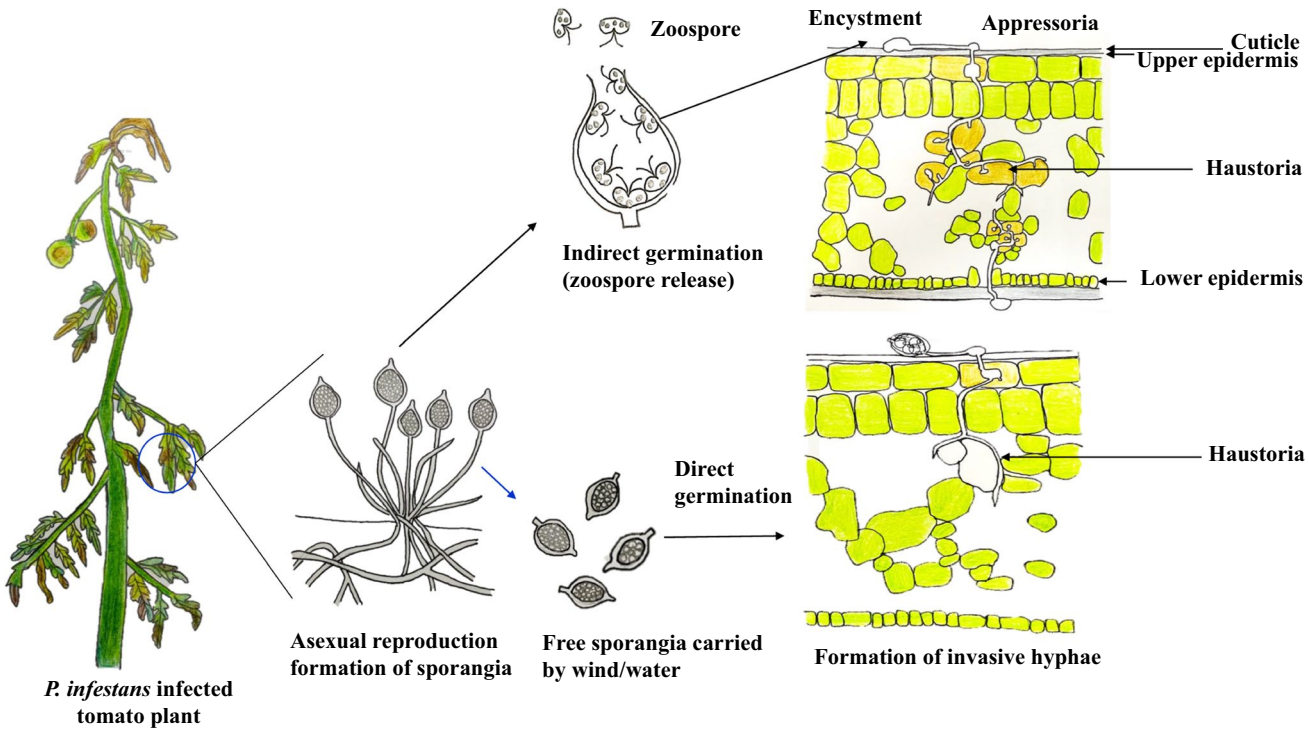

Fig. 2 Disease cycle of *Phytophthora infestans* in tomato. The diagram illustrates infection through leaves, while fruit or oospores in the soil also act as infection repositors between seasons

explained as a consequence of unique genome organization, which emphasizes the extraordinary adaptation ability of the pathogen against host plant resistance (Haas et al. 2009; Raffaele et al. 2010). In addition, host plants have evolved several strategies to shield themselves from pathogen attack. Hence, knowledge of the molecular basis of plant–pathogen interactions is essential for designing an effective strategy for controlling fast-evolving pathogens, such as *P. infestans*. In this review, we focus on recent advancements in our understanding of the molecular basis of pathogenicity between *P. infestans* and its host plant tomato and discuss the progress made regarding the identification of resistance in the host genome, effector proteins, metabolomic models, signalling process and quantitative trait loci (QTLs).

Molecular pathogenesis

Plants present several layers of immune defence. The interactions between pathogens and plant immune defence responses determines the fate of the pathogen in the host plants (Gilroy et al. 2011). The first line of immune defence against invading pathogens relies on a large family of pattern recognition receptors (PRRs), which recognize the unique evolutionarily conserved structures of pathogens known as pathogen-associated molecular patterns (PAMPs) (Altenbach and Robatzek 2007). The recognition of PAMPs by host plants induces PAMP-triggered immunity, which results in the generation of reactive oxygen species (ROS) and hypersensitive cell death in the host plant (Furuichi et al. 2014). During the infection process, host signalling processes, such as mitogen-activated protein kinases (MAPKs), are activated and modulate the expression of pathogenesis-related (*PR*) genes. However, *P. infestans* suppresses the host immune system while minimizing damage to plants because host cell integrity is crucial for its initial biotrophic lifestyle phase (Leesutthiphonchai et al. 2018). A schematic overview of the molecular pathogenesis of *P. infestans* is presented in Fig. 3. *P. infestans* has evolved several strategies to overcome PAMP-triggered immunity (PTI) by delivering immunity-suppressing molecules known as effectors to the plant. However, several of these effectors are recognized by the host plant and activate effector-triggered immunity (ETI) and subsequently programmed cell death in the host plant (Gilroy et al. 2011). The host plant ETI is mediated by a group of highly specific and conserved plant disease resistance (*R*) genes (Saunders et al. 2012a). We have discussed

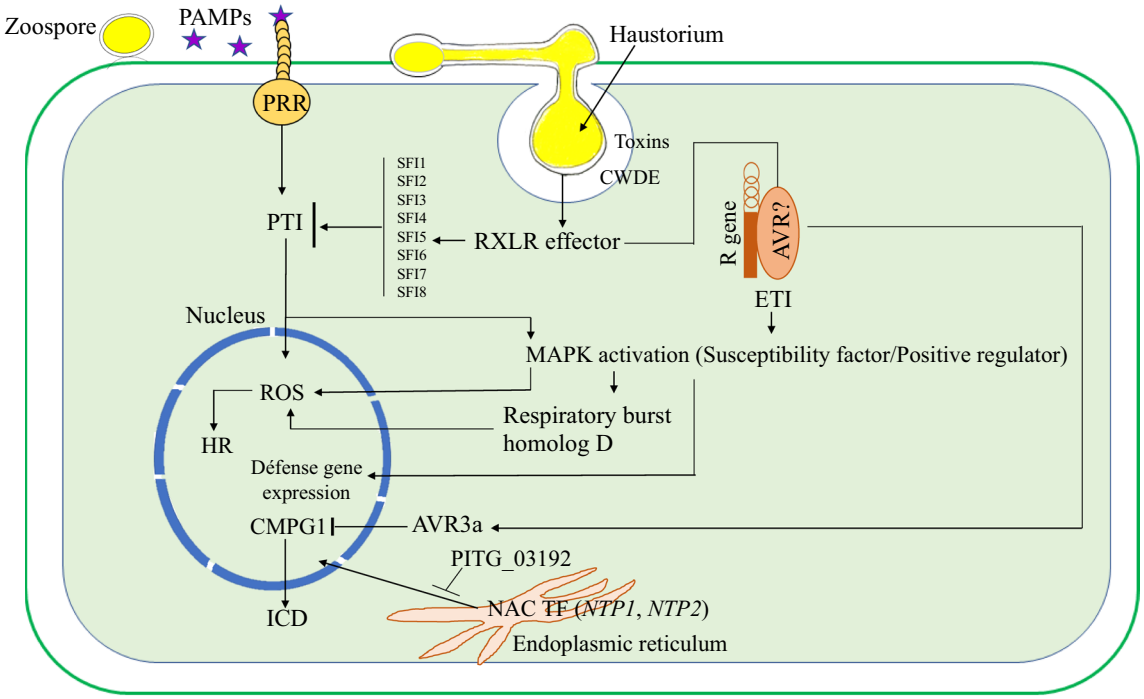

Fig. 3 Schematic model showing the molecular pathogenesis of *Phytophthora infestans*. Zoospores released from sporangium encysted and then germinated. *P. infestans* releases pathogen-associated molecular patterns (PAMPs), which are recognised by host pattern recognition receptors (PRRs), and induces PAMP-triggered immunity. To suppress PTI, *P. infestans* secretes cell wall degrading enzymes (CWDE), toxins and RXLR. Some RXLR effectors are recognised by the host resistance (*R*) gene and induce effector-triggered immunity (ETI). For simplicity, all possible steps are not shown, and only some of the characterised protein targets and activities are presented in this diagram. *AVR* avirulence, *MAPK* mitogen-activated protein kinase, *CMPG1* ubiquitin E3 ligase CMPG1, *HR* hypersensitive response, *ICD* infestin 1-triggered cell death, *ROS* reactive oxygen species

the molecular interaction between pathogens and host plants from two perspectives: from the pathogen and from the host plant.

Viewpoint from the pathogen

In the initial biotrophic phase, during which the host's immune defence and cell death are actively suppressed, pathogens produce invasive hyphae or haustoria within living plant cells (Koeck et al. 2011). Through haustoria, the pathogen derives nutrients from the host and releases a large array of effector proteins (Panstruga and Dodds 2009). Effectors can be extracellular (apoplastic) or intracellular (cytoplasmic) based on their location in plant cells (Fig. 3). Extracellular effectors are secreted in the apoplast and interact with extracellular defence-associated factors, whereas cytoplasmic effectors are transported inside the host cytoplasm and localised in various plant subcellular regions (Sharpee and Dean 2016; Wang et al. 2017).

Extracellular effectors

Extracellular effectors released by *P. infestans* are mainly of two types. The first type mediates the protection of the pathogen from host defence, and the second type mediates host invasion. Effectors that mediate protection of the pathogen from the host defence include protease inhibitors and glucanase inhibitors. Protease inhibitor effectors inhibit host-resistant proteases (Wang et al. 2019). For example, EPI1 and EPI10 effectors released by *P. infestans* inhibit the tomato subtilisin-like protease P69B (Tian et al. 2004). Similarly, EPIC1 and EPIC2B inhibit the tomato defence cysteine protease Rcr3pim (Song et al. 2009). Glucanase inhibitor proteins (GIPs) secreted by *Phytophthora* bind and inhibit the release of host extracellular endo-β-1,3-glucanases, which target the β-1,3 glucan polymers of the oomycete cell wall (Damasceno et al. 2008).

The second type of effector mediates host invasion using several approaches, including secretion of cell wall degrading enzymes (CWDEs) (Ospina-Giraldo et al. 2010; Wawra et al. 2012) and toxins (Liu et al. 2005). *P. infestans* secretes CWDEs, such as carbohydrate esterase, glycosyl hydrolases and polysaccharide lyases, which degrade the plant cell wall, thereby allowing entry of the pathogen into host tissue (Ospina-Giraldo et al. 2010). *P. infestans* also releases a group of toxins to establish infection inside the host cell. For example, *P. infestans* releases the small S locus cysteine-rich protein (SCR) family (Liu et al. 2005). The *SCR* gene family is highly similar to the *PcF* gene family, which is known for its phytotoxic necrosis-inducing role in *Phytophthora cactorum* (Chen et al. 2016). Another toxin secreted by *P. infestans* belongs to necrosis and ethylene-inducing protein 1 (Nep1)-like family (NLPs), which are involved in the damage of plasma membranes and successive cytolysis (Ottmann et al. 2009). NLPs were proposed to possess dual functions in plant-pathogen interactions, acting both as elicitors of immune responses and as toxin-like virulence factors (Qutob et al. 2006).

Elicitor is a general term that refers to molecules that act as PAMPs for the plant and subsequently induce defence responses against pathogens (Huet et al. 1994; Maffei et al. 2012). Functional characterization of the NLP protein PiNPP1.1 in *P. infestans* showed that rather than being elicitor, it acts as a toxin in *Nicotiana benthamiana* and tomato (Kanneganti et al. 2006). *P. infestans* secretes another group of toxins called elicitins (Huet et al. 1994; Derevnina et al. 2016). Elicitin are elicitors with highly conserved sterol-binding proteins with characteristics of PAMPs, secreted by oomycete pathogens (Derevnina et al. 2016). Elicitins were first demonstrated by Ricci et al. (1989) in oomycete pathogens *Phytophthora cryptogea* and *Phytophthora capsici* that elicit HR response and systemic acquired resistance in *Nicotiana* species (Ricci et al. 1989) and some radish cultivars (Keizer et al. 1998). Following that several studies have demonstrated elicitins from a diverse family of oomycete, such as cryptogein from *P. cryptogea*, capsicein from *P. capsici*, parasiticein from, and INF1 from *P. infestans* (Derevnina et al. 2016). In tomato, elicitins INF1 and INF1S3 induce basal defence, such as activation of jasmonic acid-and ethylene-mediated signalling pathways, but do not induce HR cell death or SA-mediated pathway activation (Kawamura et al. 2009). Therefore, *INF1* might act as a PAMP in tomato; however, such defence responses were not enough to suppress host colonization by *P. infestans* because tomato is susceptible to the pathogen. In addition to the abovementioned toxin, during the process of plant–pathogen interactions, *P. infestans* also secretes proteins with RGD (Arg-Gly-Asp)-containing effector protein IPI-O, which weakens the plant defence responses by damaging the interconnections between the plant cell wall and plasma membrane (Senchou et al. 2004).

Intracellular effector secreted in the cytosol of host plants

Compared with extracellular effectors, intracellular effectors are translocated after secretion into host cells (Kamoun et al. 2015). Plants have evolved resistance (*R*) genes that encode R proteins that are capable of recognizing several of these effector genes, leading to the induction of effector-triggered immunity (ETI) (Jones and Dangl 2006). This immune reaction involves a hypersensitive response, followed by programmed cell death. Among the intracellular effectors in *P. infestans*, the RXLR effector has been extensively studied, followed by the CRN effector.

RXLR effector

RXLR effectors are secreted from haustoria and translocated to the host cell (Ackerveken 2017). The RXLR effector consists of an N-terminal signal peptide and RxLR motif (where R is arginine, X is any amino acid, and L is leucine) (Wawra et al. 2017) and is often followed by another conserved motif, i.e., a dEER motif (Asp-Glu-Glu-Arg) (Win et al. 2012). The C-terminal domain mostly consists of a variable number of motifs that appear in a repeated manner (Jiang et al. 2008). The N-terminal domain of the RXLR motif is essential for secretion and targeting, while the C-terminal domain is essential for effector functions (Bos et al. 2006). Phylogenetic analyses have indicated that RXLR motifs are highly conserved and signatures of positive selection have been identified in the C-terminal region of a number of RXLR-class effectors (Win et al. 2007). Genome-wide analysis of the RXLR effector gene family in *P. infestans* has shown the presence of approximately 563 RXLR effector genes (Hass et al. 2009). Studies have shown that thirty-one RXLX effector genes are expressed during interactions between tomato and *P. infestans* (Zuluaga et al. 2016), and fourteen of these genes were novel compared to RXLX effector genes expressed during the interaction between potato and *P. infestans*. Some of these effectors have proteins that can be recognized directly or indirectly by the host plant's resistance (*R*) gene and are subsequently termed avirulence (*AVR*) genes (Petit-Houdenot and Fudal 2017). The identification of RXLR effectors and recognition that some of them act as AVR factors have driven the identification of several effector genes and their molecular interaction with AVR (Amaro et al. 2017). Knowledge of R-AVR interactions is very important for designing strategies to control oomycete diseases in plants.

Avirulence 3 (*AVR3a*) is the first functionally characterized *AVR* effector gene of *P. infestans* (Bos et al. 2010). The *AVR3a* gene has a virulent allele and an avirulent allele that differ by only two amino acids: *AVR3a* (KI) and *AVR3a* (EM) (Huang et al. 2019). *AVR3a* (KI) is recognized by the host resistance gene *R3a,* which strongly suppresses infestin 1 (INF1)-triggered cell death (ICD), and *AVR3a* (EM) eludes recognition by *R3a* and thus weakly suppresses host ICD (Bos et al. 2003; Torto et al. 2003). *AVR3a* targets and stabilizes the host ubiquitin E3 ligase CMPG1, which is necessary for inducing ICD. A mutation in the C-terminal tyrosine residue of *AVR3a* failed to suppress ICD (Bos et al. 2010). Other than *AVR3a*, another AVR effector protein of *P. infestans*, *AVRblb2*, is recognized by host plants. *AVRblb2* interferes with host immunity *by* targeting the host plant defence protease papain-like cysteine protease C14, which elevates the susceptibility of host plants to *P. infestans* by preventing its secretion into the apoplast (Bozkurt et al. 2011). The RXLR effectors SFI1, SFI2, SFI3, SFI4, SFI5, SFI6, SFI7, and SFI8 also manipulate host immunity *by* targeting PTI (Zheng et al. 2014). However, the exact molecular mechanism and plant proteins targeted by these effectors have yet to be explored.

Some effector proteins require an association with host plant proteins to initiate interactions with resistance genes. For example, *AVR2* effectors associate with the plant phosphatase *BSU-LIKE PROTEIN1* (*BSL1*) and mediate the interaction of BSL1 with plant R2 genes that activate ETI in host plants (Saunders et al. 2012b). However, virulent strains of *P. infestans* express an unrecognized form of *AVR2*-like protein that does not facilitate the association of *BSL1* with *R2* despite interacting with *BSL1*. On the other hand, some effector proteins directly manipulate defence-associated transcription regulators. For example, the RXLX effector PITG_03192 interacts with plant NAC transcription factors (*NTP1* and *NTP2*) at the endoplasmic reticulum and prevents their release from the ER to the host nucleus to enhance host susceptibility (McLellan et al. 2013). Some RXLR effectors target host susceptibility factors to promote virulence. For example, Pi04314 interacts with phosphatase 1 catalytic isoforms (Boevink et al. 2016), and Pi04089 interacts with the plant RNA-binding protein KRBP1 (Wang et al. 2015) to promote colonization. AVRblb2, another RXLX factor of *P. infestans,* interacts with host papain-like cysteine protease C14 and blocks its release to the apoplast to inhibit the degradation of virulence proteins of *Phytophthora* (Bozkurt et al. 2011). In addition, RXLR effectors such as AVR1, which is perceived by R1, interact and stabilize the exocyst component Sec5 (a subunit of the exocyst protein complex that is associated with vesicle trafficking) to enhance resistance against *P. infestans* (Du et al. 2015). Although much progress has been made in identifying several RXLR effectors, the function and molecular mechanism of many of the effectors are still unknown.

Crinkler (CRN) effector

P. infestans secretes a group of effector gene families known as Crinkler (CRN for CRinkling and Necrosis). The name is based on a typical leaf crinkling phenotype detected upon ectopic expression of two cDNAs of this group in host plants (Torto et al. 2003). Bioinformatic analysis of *Phytophthora* genomes has revealed the presence of 196 full-length genes and 255 pseudogenes in the *CRN* gene family and 10 *CRN* genes were actively expressed during *P. infestans* infection of potato (Hass et al. 2009). On the other hand, an analysis of CRN expression during *P. infestans* infection of tomato identified 51 novel CRN effector upregulations that were not found during *P. infestans*–potato infection (Zuluaga et al. 2016). This finding highlights that CRN effector expression is strongly influenced by the nature of the host. Similar to RXLR effectors, CRN proteins consist of conserved

N-terminal signal peptides followed by diverse C-terminal domains (Hass et al. 2009). The N-terminus of the CRN protein includes a characteristic ~ 50-amino-acid LXLFLAK motif and is responsible for CRN secretion and translocation into the host. The N-terminus of the CRN protein also contains an adjacent diversified DWL domain and HVLVXXP motif (Amaro et al. 2017). The C-terminus of the CRN is composed of diverse domain structures with effector and virulence functions (Schornack et al. 2010; Amaro et al. 2017). Compared with the N-termini, the C-terminal domains are highly diverse and often resemble enzymes, such as restriction endonuclease (REase), protein kinase, NTPease, HNH endonuclease, LK-nuclease and peptidase, which are predicted to be involved in toxicity determinants (Zhang et al. 2016). NTPase coupled with REase domains is common in prokaryotic organisms and mainly associated with transposable elements (Amaro et al. 2017). In *P. infestans,* the CRN coding gene *PITG_23144* showed the presence of a gypsy retrotransposon, which indicated the prokaryotic origin of the C-terminus of the CRN protein (Haas et al. 2009). Compared with the C domains, no evidence has been found for the presence of the N-terminal domain of the CRN protein among prokaryotes (Amaro et al. 2017). Although recent studies have identified and characterized several CRN virulence functions, the molecular mechanisms required for CRN secretion and translocation remain largely unknown.

Viewpoint from the plant

Plant pattern recognition receptors (PRRs) are either mostly surface-localised receptor kinases or receptor-like proteins containing several ligand-binding ectodomains that recognize PAMPs (Zipfel 2014). Several PAMPs have been reported in *P. infestans*, such as PiPE (a mycelial wall-derived PAMP derived from the surface-existing glycoprotein fructose-1,6-bisphosphate aldolase of *P. infestans*) (Furuichi et al. 2013), Nep1-like proteins (Kanneganti et al. 2006), arachidonic and eicosapentaenoic acids (Bostock et al. 2011) and elicitin (Noman et al. 2020). PTI includes a wide range of responses to impede disease progression. Initial PTI responses include the generation of ROS, activation of calcium ion signalling (Cheval et al. 2013), activation of mitogen-activated protein kinases (MAPKs), and the expression of defence-related genes (Boller and Felix 2009). However, *P. infestans* releases an array of effector proteins contributing to virulence, among which some suppress PTI, while others reprogram host cell physiology and metabolic processes to establish host colonization (Bozkurt et al. 2012; Toruño et al. 2016). On the other hand, to restrict pathogen progression, the host plant uses the second layer of the recognition system, intracellular immune receptor NB-LRR proteins, also known as R (resistance) proteins. R genes account for approximately 1–3% of the genome of tomato, potato, pepper and tobacco (Wei et al. 2016).

Resistance protein of host plant

Plant resistance proteins are encoded by a family of R genes (Malik et al. 2020). R proteins recognise pathogens directly by binding to effectors or indirectly by sensing effector-induced alterations in other proteins of the host plant (Qi and Innes 2013). The R protein is composed of a C-terminal leucine-rich repeat (LRR) domain, a highly conserved middle nucleotide-binding site (NBS) domain and a diverse N-terminal domain (Takken and Goverse 2012). The LRR domain was also reported to play a role in the autoinhibition of the receptor preceding effector interactions to keep the R proteins in the "off" state (reviewed in Qi and Innes 2013; Bentham et al. 2018). The conserved C-terminal NBS domain functions as a molecular switch for *R* gene activation via nucleotide-dependent conformational changes mediated by ADP/ATP exchange (Takken et al. 2006). The N-terminus is composed of either the TIR (Toll/interleukin-1 receptor) domain or the CC (coiled-coil) domain (Elmore et al. 2011). Both of these domains are believed to function as receptor modules required for downstream signal transduction following *R* gene activation (Takken and Goverse 2012).

The interaction of the R protein and effector is a complex process, and several models, such as the elicitor-receptor model, guard model, and decoy model, have been proposed to explain the interaction mechanism. In the elicitor-receptor model, the R protein directly recognises its corresponding AVR protein and activates defence responses in host plants (Petit-Houdenot and Fudal 2017). This model was supported by the direct binding of few R-AVR combinations. However, for many R-AVR combinations, no direct physical interactions between effectors and R proteins were observed (reviewed in van der Hoorn and Kamoun 2008). To explain the indirect interaction mechanism between the R protein and effectors, the Guard model was proposed. According to the Guard model, R proteins do not directly detect the presence of the pathogen effector but rather monitor or guard the effector's target protein in the host (Dangl and Jones 2001). Any modifications of the target by the effector lead to *R* gene activation. This model was initially proposed to explain *Pseudomonas syringae AVRPto* recognition by the tomato proteins Pto and Prf (Van der Biezen and Jones 1998), and subsequently, it was found in another effector protein (Jones and Dangl 2006). According to the Guard model, the guarded effector target is essential for the virulence function of the effector protein in the absence of the cognate R protein. However, further exploration of additional targets of AVRPto (AVR proteins of *Pseudomonas syringae* pv tomato) and AVRBs3 (family bacterial Avr proteins) demonstrated that some targets of effectors in the host act as decoys

to identify pathogen effectors via R proteins, and a decoy model was proposed (Van der Hoorn and Kamoun 2008). According to the decoy model, the guarded host protein has no defence function but imitates as a functional effector target and traps the pathogen effector and redirects it from its true targets (Grund et al. 2019). In this model, guardees will be subject to two opposing selection pressures dependent on the presence or absence of the guarding R protein. In the presence of the R protein, the guardee would be optimised for AVR interactions and hence enhance the recognition of effectors, while in the absence of the R protein, the guardee would be under pressure to evade interaction with pathogen effectors to reduce the virulence of the pathogen (Van der Hoorn and Kamoun 2008; Champouret 2010).

Interaction of *Phytophthora infestans* with the host signalling pathway

Interaction of *P. infestans* with the host activate mitogen-activated protein kinase (MAPK) cascades (Pitzschke et al. 2009). The activation of MAPK cascades plays a crucial role in activating multiple signal transduction pathways in the host plant (Murphy et al. 2018). MAPKs are composed of 3 protein kinases: MAP kinase (MAP3K), MAP2K, and MAPK. These kinases are phosphorylated in a cascading series, where MAPK is phosphorylated by MAP2K, which itself is phosphorylated by MAP3K (Ren et al. 2019). MAPKs phosphorylate several downstream molecules, including transcription factors and RESPIRATORY BURST OXIDASE HOMOLOG D, which generates ROS to induce defence responses (Asai et al. 2008). The most studied PTI activated signalling pathway is the flg22 (a fragment of bacterial flagellin)-induced signalling pathway, which recruits MAP kinase cascades (Chinchilla et al. 2007; Jelenska et al. 2017). To suppress PTI, *P. infestans* releases several effector proteins. Eight RXLR effectors, SFI1-SFI8 (suppressor of early Flg22-induced immune response, SFI), from *P. infestans* showed the potential to suppress PTI in protoplast-based assays in tomato (Zheng et al. 2014). Among these, SFI5, SFI6 and SFI7 have been shown to suppress flg22-dependent MAP kinase activation upstream of MAPK and/or at the time of MAP3K activation. This demonstrated that these effectors target the earliest stages of the MAPK signal transduction pathway in tomato. However, *P. infestans* does not possess any flagellin; therefore, the function of these RXLX effectors in attenuating flg22-mediated MAP kinase activation and induction was presumed to be related with the similarity in early targets associated with both bacterial and oomycete PAMP recognition (Zhang et al. 2014).

MAPKs either act as susceptibility factors or positive regulators during interactions with pathogen effectors. Potato vascular Highway1-Interacting Kinase (StVIK), which encodes MEK kinase (MAP3K), interacts with the RXLX effector *Pi17316* to suppress plant immunity (Murphy et al. 2018). Silencing of this MEK kinase in *N. benthamiana* attenuates *P. infestans* colonization, while transient expression of *Pi17316* in *N. benthamiana* attenuates cell death triggered by Infestin1. These findings show that MAP3K (StVIK) acts as a susceptibility factor to promote disease establishment. On the other hand, the MAP3K kinase NbMAP3Kβ2 interacts with the RXLR effector Pi22926 to incite plant immunity (Ren et al. 2019). Silencing of *NbMAP3Kβ2* in *N. benthamiana* enhanced *P. infestans* colonization and attenuated AVR4 (*Cladosporium fulvum* avirulence protein AVR4)/Cf4 (tomato resistance protein)-induced cell death, while transient and stable transgenic expression of the RXLR effector Pi22926 in *N. benthamiana* promoted leaf colonization by *P. infestans* (Ren et al. 2019). This finding showed that *NbMAP3Kβ2* acts as a positive regulator. Similarly, another MAP3K, MAPKKKε, interacts with the RXLR effector *PexRD2* and acts as a positive regulator of plant immunity. Silencing of MAPKKKε in *N. benthamiana* or expression of *PexRD2* enhances susceptibility to *P. infestans* (King et al. 2014).

Metabolic alterations mediated in host plants by *Phytophthora infestans*

Plant–pathogen interactions involve the release of pathogen-effector proteins to manipulate plant cell processes and scavenge nutrients from the host cell by the pathogen to support its growth and establishment (Rodenburg et al. 2019). Although additional data have been obtained on nutrition requisition by the pathogen, much more remains to be determined. Similar to other oomycete fungi, *P. infestans* is considered an osmotroph that extracellularly catabolises complex host nutrients, such as proteins, sugars, and fatty acids, by secreting several depolymerizing enzymes and importing the resulting simple sugars, micronutrients and amino acids into the pathogen cell (Richards et al. 2013). In addition, *P. infestans* is a hemibiotroph that requires viable host cells during the initial biotrophic stages of infection (Zuluaga et al. 2016). Hence, it produces minimal symptoms in the biotrophic phase, which is followed by a necrotrophic phase in which the lesion becomes larger and sporangia start emerging from necrotic regions (Rodenburg et al. 2019). Therefore, the physiology of the host plant changes as the infection process progresses and nutrients become available for the pathogen (Ah-Fong et al. 2017). Based on the availability of the nutrient content in the host plant, *P. infestans* adjusts its metabolism by regulating the expression of enzyme-encoding genes related to glycolytic, gluconeogenic and amino acid pathways (Judelson et al. 2009). Transcriptome mining also showed dynamics in the expression of genes encoding nutrient transporters in *P. infestans* when grown in leaves or tubers or artificial media, mainly in the

biotrophic stage, which indicates a rich influx of nutrients during the early stage of infection (Abrahamian et al. 2016). In addition to these transcriptomic studies, Rodenburg et al. (2018) proposed genome-scale metabolic models (GEMs) for *P. infestans*. By extracting information from annotated genomes (KEGG Orthology database) and introducing simulations, these authors constructed GEMs that were capable of predicting biochemical data for metabolic and genetic context and can also be used as a reference for designing future experiments to characterise the metabolism of *P. infestans*. To further understand the nutrient flux from host to pathogen during infection and the metabolic interaction of the host and pathogen, Rodenburg et al. (2019) reconstructed an integrated metabolic model of *P. infestans* and tomato (Yuan et al. 2016) by integrating two previously published models of both species. This integrated metabolic model elucidated the dynamics of pathogen–host metabolism throughout the infection process and presented information for controlling late blight infection in tomato by targeting important metabolic processes, such as thiamine biosynthesis, lipid metabolism and fatty acid biosynthesis.

Natural quantitative and qualitative resistance against *Phytophthora infestans* in tomato

The resistance of the host plant to *P. infestans* is either qualitative or quantitative. Qualitative resistance is controlled by the *resistance* (*R*) gene, while quantitative resistance is controlled by quantitative trait loci (QTLs). Approximately 68 resistance genes were identified in *Solanum* spp. against *P. infestans* (Rodewald and Trognitz 2013). Most of the resistance genes were from wild relatives of potato, such as *Solanum bulbocastanum, S. venturii, S. demissum, S. verrucosum, S. microdontum* and *S. paucissectum* (Vleeshouwers et al. 2011; Rodewald and Trognitz 2013). Additionally, several quantitative trait loci (QTLs) have been identified from both wild relative and cultivated potato species (Ghislain et al. 2001; Tan et al. 2008). Compared to potato, fewer investigations have focused on tomato because this pathogen was reported to cause more damage in potato than tomato. However, with time, *P. infestans* has undergone several genomic evolutions and thus has become one of the highly infectious pathogens of tomato (Foolad et al. 2008; Zhang et al. 2014). Natural genomic resistance to *P. infestans* has been reported in wild relatives of tomato, such as *Solanum pimpinellifolium*, *S. habrochaites* and *S. pennellii*. The resistance reported in *S. pimpinellifolium* is mainly qualitative, while the resistance reported in *S. habrochaites* and *S. pennellii* is quantitative (Merk et al. 2012). Approximately 6 resistance genes (*Ph-1*, *Ph-2, Ph-3, Ph-4, Ph-5–1* and *Ph-5–2*) have been identified in tomato and its wild relatives (Panthee et al. 2017) (Table 1). The *Ph-1* gene identified in *S. pimpinellifolium*, a wild relative of tomato, was reported to display resistance against *P. infestans* isolate T-0, and introduction of *Ph-1* into the susceptible cultivar of tomato led to improved resistance (Bonde and Murphy 1952; Gallegly and Marvel 1955). However, the resistance was gradually overcome by predominant race T1 of the pathogen (Peirce 1971; Panthee et al. 2017). The second resistance gene, *Ph-2,* was identified in another accession of *S. pimpinellifolium* (Gallegly and Marvel 1955). *Ph-2* was only able to provide partial resistance by restricting the spread of infection rather than completely eradicating the infection (Goodwin et al. 1995; Black et al. 1996). Similar to *Ph-1,* the resistance provided by *Ph-2* was also gradually overcome by novel isolates of *P. infestans* (Zhang et al. 2014), which prompted further screening for new resistance genes in tomato germplasms. Subsequently, another single partially dominant gene, *Ph-3,* was isolated from *S. pimpinellifolium* L3708 (Chunwongse et al. 2002) and a hybrid of *S. lycopersicum* CLN2037B (containing *Ph-3*) × *S. lycopersicum* LA4084 (Zhang et al. 2013), which was found to be strongly resistant to several isolates of *P. infestans* and able provide resistance when *Ph-1* and *Ph-2*-associated resistance failed. Although *Ph-3* was initially considered the most effective genetic resistance resource against *P. infestans* (Chunwongse et al. 2002), a

Table 1 Resistance genes identified in tomato and its wild relatives

Resistance gene	Chromosome	Species name	References
Ph-1	7	*Solanum pimpinellifolium*(accessions; West Virginia 19 and 731)	Bonde and Murphy (1952); Gallegly and Marvel (1955)
Ph-2	10	*Solanum pimpinellifolium*(West Virginia 700	Gallegly and Marvel (1955)
Ph-3	9	*Solanum pimpinellifolium* (accessions; L3708)	Chunwongse et al. (2002)
		Solanum lycopersicum CLN2037B (containing *Ph-3*) × *Solanum lycopersicum* LA4084	Zhang et al. (2013)
		Solanum habrochaites 'LA2099', 'LA1777' and 'LA1033	Shah et al. (2014)
Ph-4	2	*Solanum habrochaites LA1033*	Kole et al. (2006)
Ph-5–1	1	*Solanum pimpinellifolium PSLP153*	Merk et al. (2012)
Ph-5–2	10	*Solanum pimpinellifolium*	Merk et al. (2012)

few novel and more aggressive *P. infestans* isolates have also overcome the resistance provided by *Ph-3* (Foolad et al. 2008). The combination of *Ph-3* with *Ph-2* was found to successfully control aggressive strains (Merck et al. 2012). The combination of these two genes has been tested in recent tomato breeding lines (e.g., NC1 CELBR and NC2 CELBR) (Gardner and Panthee 2010), and hybrid cultivars of *S. lycopersicum*, Mountain Magic and Mountain Merit (Panthee and Gardner 2010), showed strong resistance against several isolates of *P. infestans*. The resistance gene *Ph-4* (Kole et al. 2006) was identified in *S. habrochaites* LA1033, and *Ph-5–1* and *Ph-5–2* were identified in *S. pimpinellifolium* PSLP153 (Merk et al. 2012). However, a later investigation showed that *Ph-4* is a QTL and a functional characterisation of *Ph-5* for its biological role towards resistance against *P. infestans* has yet to be determined (Panthee et al. 2017).

The qualitative resistance controlled by *R* genes is not stable because of the rapid evolution tendency of *P. infestans* (Li et al. 2011), whereas qualitative resistance controlled by quantitative trait loci is generally not specific to any race (Brun et al. 2010). Therefore, QTL identification, mapping, validation and functional characterization can aid in accelerating the map-based and/or positional cloning of resistance genes against *P. infestans*. Table 2 summarises the list of late blight resistance quantitative trait loci identified in tomato and its wild relatives. In tomato, wild *S. habrochaites* was assumed to be a potential source for high levels of quantitative non-race-specific resistance against several *P. infestans* isolates (Lobo and Navarro 1987). Resistance QTLs against *P. infestans* were identified on all twelve tomato chromosomes of the two reciprocal backcross populations derived from *S. lycopersicum* × wild *S. habrochaites* (BC-E, backcross to *S. lycopersicum*; BC-H, backcross to *S. habrochaites*) (Brouwer et al. 2004). Among them, six QTLs were found to be reliable QTLs (Table 2), as consistently detected in the replicate experiment. In another *S. habrochaites* accession, LA1777, 5 QTLs were identified, four of which were reported to be colocalised with QTLs identified by Brouwer et al. (2004), and one of them was a novel QTL. Smart et al. (2007) also reported a late blight-resistant QTL from *Lycopersicon pennellii* LA716 (now known as *S. pennellii*). Three of the QTLs reported by Brouwer et al (2004) on chromosomes 4, 5, and 11 were fine-mapped and validated using near-isogenic lines (NILs) and sub-NILs (Brouwer and St. Clair 2004), which showed that QTLs located on chromosome 5 exhibit foliar resistance while QTLs located on chromosomes 4 and 11 exhibit both foliar and stem resistance. The introgressed regions containing the resistance QTLs were also found to be linked with QTLs affecting agricultural traits, such as plant height, plant shape, maturity, yield, and fruit, which shows the possibility of linkage drag between the *S. habrochaites* resistance alleles and the phenotypical trait alleles (Brouwer and St. Clair 2004). Similar co-linkage between disease resistance QTLs were reported by Johnson et al. (2012) in two selected QTLs from *S. habrochaites* chromosomes 5 and 11 related to foliar and stem resistance against *P. infestans*. These QTLs present complex genomic organisations, including several loci that depicted pleiotropy and/or strong linkages. Subsequently, Haggard et al. (2015) re-evaluated the *P. infestans* resistance lb11 QTL identified by Brouwer and St. Clair (2004) as a probable source of quantitative resistance against *P. infestans* infection in tomato using the same sub-NILs in replicated field trials over 2 years for 17 agricultural traits, such as fruit size, shape, quality, yield, maturity, and plant architecture. The lb11 QTL was first reported via fine-mapping, where each QTL fractionated into multiple QTLs using higher resolution mapping. Approximately 34 QTLs were identified via fine-mapping among these traits, with 14% revealing a significant interaction between QTLs and the environment. Additionally, QTLs for several traits were found to be colocalised, indicating either pleiotropic effects or a strong linkage between genes regulating those traits. The association of disease resistance QTLs with phenotypical QTLs possesses both opportunities and constraints. The opportunity involves a favourable blend of *P. infestans* resistance and beneficial agricultural traits, such as that shown in the sub-NIL 08GH3999 tomato line, which can directly be used as a donor parent for marker-assisted breeding (Collard et al. 2005; Foolad and Panthee 2012) or as a parent in crossbreeding for pyramiding resistance QTL alleles with other QTL donor lines to escalate the quantitative resistance level against *P. infestans* infection (Collard and Mackill 2008; Brouwer and St. Clair 2010). Constraints involve the combination of *P. infestans* resistance and undesirable agricultural traits, such as that displayed in the sub-NIL 08GH8032 tomato lines, which show higher foliar resistance but shorter and wider fruit shapes and smaller ripe fruit perimeters with delayed maturity. Therefore, the use of such QTLs in tomato breeding requires separation from negative effects through recombination, which requires testing of thousands of progeny to recover favourable recombinants (Haggard et al. 2015).

Generation of resistance against *Phytophthora infestans* in tomato via a transgenic approach

The generation of resistant varieties using plant transformation is a faster approach than traditional breeding. The availability of several efficient regeneration systems amenable to plant transformation systems (Abu-El-Heba et al. 2008; Hoshikawa et al. 2019) and the recently developed CRISPR-mediated genome editing system (Danilo et al. 2019; Ghorbani et al. 2020) for tomato varieties has opened up wider opportunities for testing the function of several stress-related genes as well as the generation of resistant

Table 2 Summary of late blight resistance quantitative trait loci detected in tomato and its wild relatives

Name of QTLs	*Phytophthora infestans* strain	Chromosome	Position in chromosome (cM)	Flanking markers/nearest marker	Mapping population	Molecular markers	References
lb1a	*P. infestans* 7629 (A1, US-6 genotype) and 9175 (A1 mating type, -resistant, US-11 genotype)	1	0–40	CT233-TG273	Reciprocal backcross populations *Solanum lycopersicum* (late blight susceptible × wild *Solanum habrochaites* (BC-E, backcross to *Solanum lycopersicum*)	RFLPs	Brouwer et al. (2004)
lb3		3	9–49	TG56-TG42			
lb4		4	0–52	TG15-CT173			
lb5b		5	31–64	CT93-TG185			
lb11b		11	27–67	TG194-TG393			
lb5ab		5	12–80	CT101-TG69	BC-H, backcross to *Solanum habrochaites*		
lb6ab		6	19–72	CT216-TG221			
–	*P. infestans* US980025 (Cornell University Phytophthora culture collection) and US970001 (American Type Culture Collection no. MYA-2350)	6	50–60	T1556	*Lycopersicon pennellii LA716*	SNP	Smart et al. (2007)
–	*P. infestans*_6_A1	9	64.0	solcap_snp_sl_29196	Line NC 2 CELBR (homozygous for the late-blight resistant alleles at both *Ph-2* and *Ph-3*, which produces large fruits) × Heirloom cultivar called 'Koralik' (which produces small, sweet fruits)	SNP	Brekke et al. (2019)
–	*P. infestans* 8_A1	11	78.1	solcap_snp_sl_2671			
–	*P. infestans* US-23	9	0.67	solcap_snp_sl_69978	F2 crossings of NC 1CELBR × Fla. 7775	SNP	Panthee et al. (2017)
		10	0.64	solcap_snp_sl_8807			
–	*P. infestans* isolate RS2009T1, belonging to race T-1, mating type A1	2	0.0	S041728	LB-susceptible tomato breeding line (Fla. 8059) × PI 163,245 was screened for LB resistance	SNP	Ohlson et al. (2018)
			0.0	S043233			
			6.7	S044782			
			8.1	S048832, S053579			
			9.5	S054749			
			16.4	S055431			
			25.5	S055792			
		3	78.4	S073679			
		10	93.5	S195527			
		11	0.0	S196053			
–	*P. infestans* Pi733	2	13.7	02g30827526	Tomato accession L3708 (*Solanum pimpinellifolium* L.)	SNP	Chen et al. (2014)
	P. infestans Pi733, Pi39A	9	116.4	09g66864250			

Table 2 (continued)

Name of QTLs	*Phytophthora infestans* strain	Chromosome	Position in chromosome (cM)	Flanking markers/nearest marker	Mapping population	Molecular markers	References
Rlbq4a	*P. infestans* isolates T1,2 and T1,2,4	4	–	–	*Solanum habrochaites* LA1777	SNP	Li et al. (2011)
Rlbq4b		4					
Rlbq7		7					
Rlbq8		8					
Rlbq12		12					

varieties. Overexpression of several antifungal genes from resistant wild relatives, transcription factors, defence-related genes, and *R* genes and silencing of negative regulators, such as microRNA and circular RNA, have shown promising results for the development of resistance against *P. infestans* in tomato (Table 3).

Expression of antifungal genes

The expression of antifungal genes is the most common approach for addressing oomycete diseases in plants. The expression of antifungal Kiwi pathogenesis-related group 5 (PR-5) proteins in tomato showed improved resistance against *P. infestans* (Korneeva et al. 2010). Pathogenesis-related (PR) proteins are induced and accumulate in host plants in the event of pathogen attack (Jain and Khurana 2018). Chitins are β-1,4-like polymers of N-acetylglucosamine polysaccharides and primary components of cell walls in fungus (Elsoud and Kady 2019). Although a putative chitin synthase (*CHS*) gene is present in the genome, the presence of chitin has not been detected in the cell wall of *P. infestans* (Guerriero et al. 2010; Hinkel et al. 2017). A study on ectopic expression of chitin-binding genes from *Amaranthus caudatus (ac)*, *A. retraflexus (RS-intron-Shir)* and hevein-like antimicrobial peptides *(amp1* and *amp2)* from *Stellaria media* in tomato plants showed enhanced resistance against *P. infestans* (Khaliluev et al. 2011). However, the mechanism by which chitin-binding genes enhances resistance in tomato were not well explained.

Expression of defence-related genes

The expression of defence-related genes is another approach to elevating disease resistance. Overexpression of the potato *R1* resistance gene (Faino et al. 2010), *S. bulbocastanum R* gene (*Rpi-bIb1*) (Van Der Vossen et al. 2003) and *S. pimpinellifolium R1* gene (Jiang et al. 2018a) in tomato showed significantly improved resistance. However, tomato plants that overexpressed the potato *R1* resistance gene (*S. lycopersicum* cv Moneymaker and cv San Marzano) showed improved resistance only against IPO-0, an isolate of *P. infestans,* and displayed susceptibility to another isolate, 88,133 (Faino et al. 2010). This study provided evidence indicating that the use of a single *R* gene is not a sustainable approach to achieving resistance against fast-evolving pathogens, such as *P. infestans*. Overexpression of two phytoalexin genes of grapevine (*Vitis vinifera*) *stilbene synthase* (*vst1* and *vst2*) in tomato showed significant improvements in resistance against *P. infestans* (Table 3). *Stilbene synthase* catalyses the biosynthesis of stilbene phytoalexin trans-resveratrol, which is known for its active role in plant defence mechanisms (Parage et al. 2012).

Table 3 Transgenic tomato lines developed against *Phytophthora infestans*

Tomato cultivars	Transformation method	Gene name	Gene source	Gene function	Types of expression	*Phytophthora infestans* strain	Effect	References
Solanum lycopersicum L	*Agrobacterium* mediated transformation	*PR-5*	Kiwi	Pathogenesis-related group 5 (PR-5) proteins, an antifungal, acidic thaumatin-like protein	Overexpression	No strain specified	Transgenic tomato plants that overexpressed PR-5 protein genes showed improved resistance against *P. infestans* compared to wild type	Korneeva et al. (2010)
Solanum lycopersicum L *line YaLF*	*Agrobacterium* mediated transformation	Chitin-binding proteins from *Amaranthus caudatus* (*ac*) and *A. retraflexus* (*RSintronShir*) and heveinlike antimicrobial peptides (*amp1* and *amp2*) from *Stellaria media*	*Amaranthus caudatus; A. retraflexus; Stellaria media*	Chitin-binding proteins	Chitin-binding protein possess fungicidal activity	Strain name not specified	Transgenic tomato plants that overexpressed genes *ac, amp1*, and *amp2* showed improved resistance against *P Infestans*	Khaliluev et al. (2011)
Solanum lycopersicum cv Moneymaker and cv San Marzano	*Agrobacterium* mediated transformation	Potato *R1* resistance gene	*Solanum demissum*	*R1* resistance gene is a member of the leucine zipper/NBS/LRR class of plant resistance genes	Overexpression	*P. infestans* isolate 88,133 and IPO	Transgenic line showed significant increase in the resistance against *P. infestans* isolate IPO-0 while susceptible to isolate 88,133	Faino et al. (2010)
Solanum lycopersicum cv Moneymaker	*Agrobacterium* mediated transformation	*Solanum bulbocastanum R* gene (*RpibIb1*)	*Solanum bulbocastanum*	*Rpi-bIb1* gene is a member of CC-NBS-LRR class of plant resistance gene	Overexpression	*P. infestans* isolate IPO665-2A and IPO428	Transgenic line showed significant increase in the resistance against *P. infestans* isolate compared to wild type	Van Der Vossen et al. (2003)
Solanum lycopersicum Zaofen No.2	*Agrobacterium* mediated transformation	Resistant gene (SpNBS-LRR) protein in tomato)	*Solanum pimpinellifolium* L3708	Resistance (*R*) gene	Overexpression	*P. infestans P12103*	Transgenic tomato plants that overexpressed SpNBS-LRR showed improved resistance compared to wild-type plants after infection with *P. infestans*	Jiang et al. (2018a)

Table 3 (continued)

Tomato cultivars	Transformation method	Gene name	Gene source	Gene function	Types of expression	*Phytophthora infestans* strain	Effect	References
Solanum lycopersicum cv. Haubners' Vollendung	*Agrobacterium* mediated transformation	*Stilbene synthase* (*vst1*and *vst2*)	Grapevine (*Vitis vinifera*)	Resveratrol, a phytoalexins is synthesized by the enzyme stilbene synthase	Overexpression	No strain specified	Transgenic line showed significant increase in the resistance against *P. infestans* isolate	Thomzik et al. (1997)
Solanum lycopersicum cv. Zaofen No. 2	*Agrobacterium* mediated transformation	*SpWRKY1*	*Solanum pimpinellifolium* L3708	*SpWRKY1* is a transcription factor associated with biotic stress	Overexpression	*P. infestans P12103*	Transgenic tomato plants that overexpressed a pathogen induced *SpWRKY1* gene from the wild tomato *Solanum pimpinellifolium* L3708 in cultivated tomato showed improved resistance against *P infestans* compared to wild-type plant	Li et al. (2015)
Solanum lycopersicum Zaofen No.2	*Agrobacterium* mediated transformation	*SpWRKY3*	*Solanum pimpinellifolium* L3708	*SpWRKY3* induces *PR* gene expression	Overexpression and silencing	No strain specified	Tomato plants that overexpressed *SpWRKY3* showed improved resistance against *P. infestans*, while the silenced lines showed impaired resistance	Cui et al. (2018b)
Solanum lycopersicum Zaofen No.2	*Agrobacterium* mediated transformation	*SpWRKY6*	*Solanum pimpinellifolium* (L.) Mill. cv. L3708	*SpWRKY6* induces PR gene expression	Overexpression or gene silencing	No strain specified	Tomato plants that overexpressed *SpWRKY* showed improved resistance against *P. infestans* while inhibition of *SpWRKY6*mRNA accumulation in tomato leaves, using virus-induced gene silencing (VIGS) significantly impaired tomato resistance against *P. infestans*	Hong et al. (2018)

Table 3 (continued)

Tomato cultivars	Transformation method	Gene name	Gene source	Gene function	Types of expression	*Phytophthora infestans* strain	Effect	References
Solanum lycopersicum Zaofen no. 2	*Agrobacterium* mediated transformation	*MYB49* (*Solyc10g008700.1*)	*Solanum lycopersicum* Zaofen no. 2	*MYB49* is a transcription factor associated with biotic stress	Overexpression	No strain specified	Tomato plants that overexpressed *MYB49* showed enhanced the resistance against *P. infestans* compared to wild type	Cui et al. (2018a)
Solanum lycopersicum cv. Moneymaker	*Agrobacterium* mediated transformation	Defense No Death 1 (DND1)	*Solanum lycopersicum* cultivar Moneymaker	Defense No Death 1 (DND1) is susceptibility gene, it encodes a mutated cyclic nucleotide-gated ion channel and act as susceptibility factor	RNAi	*P infestans* isolate Pic99189	Silencing of the *DND1* in tomato plants improve resistance against *P. infestans*	Sun et al. (2016)
Solanum lycopersicum cv. Zaofen No.2	*Agrobacterium* mediated transformation	MiRNA396a-5p and -3p	*Solanum lycopersicum cv. Zaofen No.2*	MiRNA396a-5p and -3p supresses growth-regulating factor1 (GRF1), salicylic acid carboxyl methyltransferase (SAMT), glycosyl hydrolases (GH) and nucleotide-binding site-leucine-rich repeat (NBS-LRR)	Overexpression	Strain name not specified	Tomato plants that overexpressed miR396a-5p and -3p impaired resistance against *P. infestans*	Chen et al. (2017)
Solanum lycopersicum cv. Zaofen No.2	*Agrobacterium* mediated transformation	MIR1916 precursor	*Solanum lycopersicum cv. Zaofen No.2*	sly-miR1916 represses *Strictosidine synthase* (*STR-2*), *UDP-glycosyltransferases* (*UGTs*), late blight resistance protein homolog *R1B-16*, disease resistance protein *RPP13-like*, and MYB transcription factor (*MYB12*)	Overexpression and silencing (short tandem target mimic and artificial microRNA)	Strain name not specified	Tomato plants that overexpressed miR1916 showed impaired resistance against *P. infestans* while silencing improved resistance	Chen et al. (2018)

Table 3 (continued)

Tomato cultivars	Transformation method	Gene name	Gene source	Gene function	Types of expression	*Phytophthora infestans* strain	Effect	References
Solanum lycopersicum Zaofen No. 2	Agrobacterium mediated transformation	MiRNA482a, Sl-lncRNA15492,	*Zaofen No. 2*	lncRNAs inhibits the precursor miRNA482a expression	Overexpression and silencing (STTMs and reverse amiRNAs)		Sl-lncRNA15492 regulates tomato resistance via inhibiting negative regulator Sl-miR482a. Sl-miR482a negatively regulate tomato resistance by targeting Sl-NBS-LRR genes	Jiang et al. (2020)
Solanum pimpinellifolium L3708	*Agrobacterium* mediated transformation	MiR482b precursor	*Solanum pimpinellifolium* L3708	MiR482b suppresses 30 NBS-LRRs gene	Overexpression and silencing	*P. infestans* P12103	Tomato plants that overexpressed miR482b showed more severe disease symptoms compared to wild type while silencing of miR482b resulted enhancement of tomato resistance against *P. infestans*	Jiang et al. (2018b)
Solanum lycopersicum Zaofen No. 2	*Agrobacterium* mediated transformation	MiR482c precursor	*Solanum lycopersicum* Zaofen No. 2	*MiR482c* targets two R (NBS-LRR) genes with coiled-coil domains (CNLs); Solyc07g049700 and Solyc11g006530	Overexpression	*P. infestans* P12103	Tomato plants that overexpressed miR482c showed weaken plant resistance against *P. infestans*	Hong et al. (2019)
Solanum lycopersicum Zaofen No.2	*Agrobacterium* mediated transformation	MiR1918 precursor	Synthesised Arabidopsis thaliana pre-miR159a as a backbone	*MiR1918* suppresses RING finger gene	Overexpression	*P. infestans* P12103	Transgenic tomato plants that overexpressed the artificial pi-miR1918 showed more severe disease symptoms than wild-type tomato plants after infection with *P. infestans*	Luan et al. (2016)

Table 3 (continued)

Tomato cultivars	Transformation method	Gene name	Gene source	Gene function	Types of expression	*Phytophthora infestans* strain	Effect	References
Solanum lycopersicum Zaofen No. 2	*Agrobacterium* mediated transformation	MiR172a and b precursor	*Solanum pimpinellifolium* L3708	*MiR172a* and *b* suppresses an *AP2/ERF* transcription factor	Overexpression	*P. infestans* P12103	Tomato plants that overexpressed miR172a and b in tomato increased resistance against *P. infestans* infection by suppressing of an AP2/ERF transcription factor	Luan et al. (2018)
Solanum lycopersicum Zaofen No.2	*Agrobacterium* mediated transformation	lncRNA33732	*Solanum lycopersicum Zaofen No.2*	lncRNA33732 regulates the expression of respiratory burst oxidase (RBOH; Solyc08g081690.2.1)	Overexpression	*P. infestans P12103*	The overexpression and silencing analysis of lncRNA33732 in tomato showed that lncRNA33732 is positive regulator and enhanced tomato resistance *to P. infestans*	Cui et al. (2019)
Solanum pimpinellifolium L3708	Agrobacterium mediated transformation	Circular RNAs (circRNA45 and circRNA47)	*Solanum pimpinellifolium* L3708	*CircRNA45* and *circRNA47* acted as miR477-3p sponges and regulate tomato resistance	Transient transformation of leaf	*P. infestans strain P12103*	Tomato plants that transiently overexpressed circRNA45 and circRNA47 both showed improved resistance against *P. infestans* accompanied by lower expression levels of miR477-3p	Hong et al. (2020)

Manipulation (overexpression/silencing) of transcription factors

Overexpression of transcription factor (TF) genes, such as *WRKY* and *MYB*, also shows significant enhancement in resistance against *P. infestans.* Transcription factors are important components in the signalling system and have been involved in mainly positive but sometimes negative regulatory processes underlying stress responses in plants by inducing and/or repressing the expression of an array of downstream defence-related genes (Ma et al. 2013; Tian et al. 2015). The WRKY family is an example of a positive stress regulator TF that is mainly associated with diverse biotic stresses (Pandey and Somssich 2009). Overexpression of *S. pimpinellifolium WRKY1* (*SpWRKY1)* in the susceptible cultivated tomato cultivar Zaofen No. 2 showed a significant reduction in cell death, ROS accumulation, lipid peroxidation and relative electrolyte leakage and an increase in ROS scavenging antioxidant enzyme activity (peroxidase, superoxide dismutase, phenylalanine ammonia-lyase) compared to the wild type (Li et al. 2015). The overexpression of *SpWRKY1* also upregulated other downstream defence-related genes, such as ROS scavenging-related genes and salicylic acid/jasmonic acid-responsive genes, in transgenic lines (Cui et al. 2019). Similarly, overexpression of *SpWRKY3* (Cui et al. 2018b) and *SpWRKY6* (Hong et al. 2018) also showed promising enhancement in resistance in tomato plants against *P. infestans* (Table 3). *SpWRKY3* and *SpWRKY6* overexpression showed elevated resistance, which is evidence of lower necrosis, small lesion sizes, less ROS generation and a low disease index, while the silenced lines showed more severe disease symptoms than the wild-type lines. Furthermore, the overexpression lines after inoculation with *P. infestans* infection showed upregulated pathogenesis-related (*PR*) gene expression in transgenic tomato plants compared to wild-type plants.

In addition to *WRKYs*, *MYB* TFs are also known for their crucial role in increasing the susceptibility of plants to biotic stresses (Erpen et al. 2017). Overexpression of native *MYB49* in the susceptible tomato cultivar *S. lycopersicum* Zaofen no. 2 significantly enhanced resistance against *P. infestans*, as evidenced by lower necrosis, small lesion size and lower disease index (Cui et al. 2018a). Compared to the wild-type control plants, the transgenic lines showed higher accumulation of ROS and malonaldehyde content and lowered relative electrolyte leakage and higher activity of ROS scavenging enzymes (peroxidase and superoxide dismutase) upon *P. infestans* inoculation. Although some of the TFs are reported to have a significant response against *P. infestans*, a vast majority of the TF family remains unexplored. For example, the role of biotic stress-related TFs, including ERF and bZIP, has been reported in response to *P. infestans* in potato. ERF was reported to act as a negative stress regulator in potato. Transgenic potato lines with silenced ERF (*StERF3*) showed significant enhancement in resistance against *P. infestans* (Tian et al. 2015). Moreover, bZIPs were reported to act as positive stress regulators in potato, and potato overexpressing bZIP (*Stb ZIP 61*) (Zhou et al. 2018) showed significant enhancement in resistance against *P. infestans.* Hence, the TFs *ERF* and *bZIP* can also be explored in tomato in response to *P. infestans.*

Silencing of susceptibility genes

Silencing of the negative regulator is another approach to improving resistance. Plant genes that facilitate infection and aid in the compatibility of the host are known as susceptibility (*S*) genes (van Schie and Takken 2014). Silencing of such an *S* gene *Defense No Death 1* (DND1) in tomato plants (*S. lycopersicum* cultivar Moneymaker) showed remarkably increased resistance against *P. infestans* (Sun et al. 2016).

Manipulation of non-coding genes

In addition to functional genes, manipulation of non-coding genes, such as microRNAs (miRNAs), long non-coding RNAs and circular RNAs, was also reported to be useful for improving resistance in tomato plants against *P. infestans*. MiRNAs are a class of endogenous small non-coding RNAs of approximately 22 -24 nucleotides that post-transcriptionally regulate the expression of genes via translational repression or mRNA degradation (Cai et al. 2009). miRNAs can regulate both positive and negative resistance genes. Negatively regulated miRNAs are downregulated during biotic stress in resistant plants, while positively regulated miRNAs are upregulated (Chauhan et al. 2017). Therefore, miRNAs serve as a potential alternative resource to be used for the control of plant pathogens.

Several tomato miRNAs, such as miR396a-5p and -3p, miR1916, miR482a, miR482b, miR482c and miR4773p, are actively involved in interactions between tomato and *P. infestans* and negatively affect tomato resistance by targeting mainly *R* gene (NBS-LRR) genes. Infection of *P. infestans* in tomato plants downregulates the expression of miR396a-5p and miR396a-3p (Chen et al. 2017) and MiR1916 (Chen et al. 2018). MiR396a-5p targets *growth-regulating factor* (*GRF*) genes (Chen et al. 2017), while miR1916 targets strictosidine synthases, uridine diphosphate-glycosyltransferases, disease resistance protein RPP13-like, late blight resistance protein homologue *R1B-16* and *MYB 12* (Chen et al. 2018). Overexpression of miR396a-5p and miR396a-3p in tomato plants increases the susceptibility to *P. infestans,* as evidenced by lower necrosis and higher ROS compared to the wild type (Chen et al. 2017). Similarly, overexpression of miR1916 in transgenic tomato also increases susceptibility to late blight infection, while silencing of miR1916 improves

tolerance (Chen et al. 2018). Overexpression of another negative regulator, miR482a (Jiang et al. 2020) and miR482b (Jiang et al. 2018b), in tomato plants showed impairment in resistance against *P. infestans,* while silencing resulted in improvement in tomato resistance. Similar impairment in resistance was observed for miR482c-overexpressing tomato lines, where the transgenic plants showed reduced activity of ROS scavenging enzymes (peroxidase, superoxide dismutase and phenylalanine ammonia-lyase) and higher lipid peroxidation than wild-type tomato plants. The overexpressed lines showed downregulation of target resistance genes (*NBS-LRR*): *Solyc07 g049700* and *Solyc11 g006530*. Additionally, for another miRNA, miR1918, transgenic tomato lines overexpressing artificial pi-miR1918 exhibited a higher infection rate than wild-type plants upon inoculation with *P. infestans,* which indicates that miR1918 increases the susceptibility of tomato plants to *P. infestans* (Hong et al. 2019).

In contrast to negative regulator miRNAs, few miRNAs act as positive regulators in tomato stress resistance. Overexpression of miR172a and b in the susceptible tomato cultivar Zaofen No. 2 significantly improved resistance against *P. infestans* by suppressing the AP2/ERF transcription factor (*Solyc11 g072600.1.1*). The overexpressed line displayed a lower disease index, smaller lesion sizes, lower ROS, lower lipid peroxidation levels but higher activities of ROS scavenging enzymes (POD and SOD) and photosynthetic rates (Luan et al. 2018).

In addition to miRNAs, long non-coding RNAs also regulate plant resistance. Long non-coding RNAs are a group of non-coding RNA molecules that are longer than 200 nucleotides (Kung et al. 2013). MiRNAs cleave long non-coding RNAs and generate phased small interfering RNAs, which compete with endogenous RNAs and act as decoys for mature miRNAs, leading to re-expression of miRNA target genes (Ratti et al. 2020). In tomato, a long non-coding RNA, Sl-lncRNA15492 (511 bp), was reported to repress the negative stress regulator miR482a, whose precursor was placed within the Sl-lncRNA15492 antisense sequence (Jiang et al. 2020). Degradome analysis followed by RLM-5′ RACE experiments showed that mature Sl-miR482a might also cleave Sl-lncRNA15492. This shows that Sl-lncRNAS15492 and Sl-miR482a reciprocally destroy Sl-NBS-LRR1 homeostasis during the process of tomato plant resistance against *P. infestans*.

Circular RNAs (circRNAs) are long non-coding RNAs whose 5' and 3' termini are covalently linked, and because of their capacity to bind microRNAs (miRNAs), they also serve as miRNA sponges (Yu and Kuo 2019). In silico analysis detected a total of 68 circRNAs, of which 9 were reported to be upregulated during the *P. infestans* infection process in tomato plants (Hong et al. 2020). Among them, circRNA45 and circRNA47, transiently overexpressed in tomato plants, displayed smaller lesion areas in both transgenic lines compared to wild-type plants upon *P. infestans* infection. CircRNA45 and circRNA47 act as sponges for the negative regulator miR477-3p, which might be the main reason behind the improvement in resistance, as evident by the low expression of miR477-3p.

Conclusion and future prospects

P. infestans has become a devastating pathogen to control even 180 years after its identification because of its tremendous ability to overcome host resistance. By mining the literature on *P. infestans* and tomato interactions, we observed the involvement of multiple cell wall-degrading enzymes, effectors of pathogens and host resistance genes, kinases, transcription factors and non-coding RNAs in the molecular interactions underlying pathogenesis. The molecular interactions between *P. infestans* virulence and host resistance drive the coevolution of the pathogen as well as the host genome. *R* genes exert selection pressure on pathogens to improve their virulence through the modification of the pathogen *AVR* gene inventory to overcome host plant defence. To date, approximately 6 resistance genes/genomic regions have been identified in tomato and its wild relatives (Table 1), most of which have already been overcome by aggressive isolates of *P. infestans.* At present, the combination of *Ph-3* with *Ph-2* is the most successful. Hence, detailed research is needed to screen new resistance genes in tomato germplasms. Several QTLs were identified, although few of them have been validated (Table 2). Several QTLs were found to be linked with other phenotypic traits. Validated QTLs with favourable phenotypic traits will be promising candidates for use in *P. infestans* resistance breeding programs in tomato. Much progress has been made in elucidating tomato metabolome manipulation by *P. infestans*. Based on that, an integrated host–pathogen genome-scale metabolic model was proposed that can be used for further exploration of plant–oomycete metabolic interactions and identification of novel defence or oomycete genes. Overexpression of several antifungal genes, defence-related genes, and long non-coding RNAs and silencing of negative regulators, such as susceptibility genes or miRNAs, showed improvement in resistance in transgenic tomato lines (Table 3). However, for a fast-evolving pathogen such as *P. infestans*, a more strategic approach is needed, such as stacking multiple genes with a suitable combination along with or silencing of negative regulators. With advancements in sequencing technology, genomes of both the pathogen and host plant tomato are now available in public domains and efficient transformation and genome editing systems are reported. These resources provide an opportunity to explore further the functions and networks of effectors, regulatory genes, defence genes and non-coding RNAs associated with pathogenesis, along with

evolutionary insight to design targeted strategies to eliminate late blight in tomato.

Author contribution statement PM has designed the outline of the article, composed the manuscript and figure. NR and PS provided feedback and comments to revise the content. DK has assisted with artwork and ID has provided field image. All the authors read and approved the manuscript.

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Declarations

Conflict of interest The authors declare that they have no competing interests.

References

Abrahamian M, Ah-Fong AM, Davis C, Andreeva K, Judelson HS (2016) Gene expression and silencing studies in *Phytophthora infestans* reveal infection-specific nutrient transporters and a role for the nitrate reductase pathway in plant pathogenesis. PLoS Pathog 12(12):e1006097. https://doi.org/10.1371/journal.ppat.1006097

Abu-El-Heba GA, Hussein GM, Abdalla NA (2008) A rapid and efficient tomato regeneration and transformation system. Landbauforschung Volkenrode 58:103–110

Ackerveken G (2017) Seeing is believing: imaging the delivery of pathogen effectors during plant infection. New Phytol 216(1):8–10. https://doi.org/10.1111/nph.14755

Ah-Fong AM, Kim KS, Judelson HS (2017) RNA-seq of life stages of the oomycete *Phytophthora infestans* reveals dynamic changes in metabolic, signal transduction, and pathogenesis genes and a major role for calcium signalling in development. BMC Genomics 18(1):198. https://doi.org/10.1186/s12864-017-3585-x

Altenbach D, Robatzek S (2007) Pattern recognition receptors: from the cell surface to intracellular dynamics. Mol Plant-Microbe Interact 20(9):1031–1039. https://doi.org/10.1094/MPMI-20-9-1031

Amaro TM, Thilliez GJ, Motion GB, Huitema E (2017) A perspective on CRN proteins in the genomics age: evolution, classification, delivery and function revisited. Front Plant Sci 8:99. https://doi.org/10.3389/fpls.2017.00099

Asai S, Ohta K, Yoshioka H (2008) MAPK signaling regulates nitric oxide and NADPH oxidase-dependent oxidative bursts in *Nicotiana benthamiana*. Plant Cell 20(5):1390–1406. https://doi.org/10.1105/tpc.107.055855

Aylor DE (2003) Spread of plant disease on a continental scale: role of aerial dispersal of pathogens. Ecology 84:1989–1997. https://doi.org/10.1890/01-0619

Bentham AR, Zdrzałek R, Dela Concepcion JC, Banfield MJ (2018) Uncoiling CNLs: structure/function approaches to understanding CC domain function in plant NLRs. Plant and Cell Physiol 59(12):2398–2408. https://doi.org/10.1093/pcp/pcy185

Black LL, Wang TC, Hanson PM, Chen JT (1996) Late blight resistance in four wild tomato accessions: effectiveness in diverse locations and inheritance of resistance. Phytopathol 86:S24. https://doi.org/10.1007/s10681-005-9079-y

Boevink PC, Wang X, McLellan H, He Q, Naqvi S, Armstrong MR, Zhang W, Hein I, Gilroy EM, Tian Z, Birch PR (2016) A *Phytophthora infestans* RXLR effector targets plant PP1c isoforms that promote late blight disease. Nature Commun 7(1):1–4. https://doi.org/10.1038/ncomms10311

Boller T, Felix G (2009) A renaissance of elicitors: perception of microbe-associated molecular patterns and danger signals by pattern-recognition receptors. Annu Rev Plant Biol 60:379–406. https://doi.org/10.1146/annurev.arplant.57.032905.105346

Bonde R, Murphy EF (1952) Resistance of certain tomato varieties and crosses to late blight. Maine Agr Exp Sta Bull 497:5–15

Bos JIB, Armstrong M, Whisson SC, Torto TA, Ochwo M, Birch PRJ, Kamoun S (2003) Intraspecific comparative genomics to identify avirulence genes from *Phytophthora*. New Phytol 159:63–72. https://doi.org/10.1046/j.1469-8137.2003.00801.x

Bos JI, Kanneganti TD, Young C, Cakir C, Huitema E, Win J, Armstrong MR, Birch PR, Kamoun S (2006) The C-terminal half of *Phytophthora infestans* RXLR effector AVR3a is sufficient to trigger R3a-mediated hypersensitivity and suppress INF1-induced cell death in *Nicotiana benthamiana*. The Plant J 48(2):165–176. https://doi.org/10.1111/j.1365-313X.2006.02866.x

Bos JI, Armstrong MR, Gilroy EM, Boevink PC, Hein I, Taylor RM, Zhendong T, Engelhardt S, Vetukuri RR, Harrower B, Dixelius C (2010) *Phytophthora infestans* effector AVR3a is essential for virulence and manipulates plant immunity by stabilizing host E3 ligase CMPG1. Proc Natl Acad Sci USA 107(21):9909–9914. https://doi.org/10.1073/pnas.0914408107

Bostock RM, Savchenko T, Lazarus C, Dehesh K (2011) Eicosapolyenoic acids: novel MAMPs with reciprocal effect on oomycete-plant defense signaling networks. Plant Signal Behav 6(4):531–533. https://doi.org/10.4161/psb.6.4.14782

Botero D, Valdés I, Rodríguez MJ, Henao D, Danies G, González AF, Restrepo S (2018) A genome-scale metabolic reconstruction of *Phytophthora infestans* with the integration of transcriptional data reveals the key metabolic patterns involved in the interaction of its host. Front Genet 10(9):244. https://doi.org/10.3389/fgene.2018.00244

Bozkurt TO, Schornack S, Win J, Shindo T, Ilyas M, Oliva R, Cano LM, Jones AM, Huitema E, van der Hoorn RA, Kamoun S (2011) *Phytophthora infestans* effector *AVRblb2* prevents secretion of a plant immune protease at the haustorial interface. Proc Natl Acad Sci USA 108(51):20832–20837. https://doi.org/10.1073/pnas.1112708109

Bozkurt TO, Schornack S, Banfield MJ, Kamoun S (2012) Oomycetes, effectors, and all that jazz. Curr Opin Plant Biol 15:483–492. https://doi.org/10.1016/j.pbi.2012.03.008

Brekke TD, Stroud JA, Shaw DS, Crawford S, Steele KA (2019) QTL mapping in salad tomatoes. Euphytica 215(7):115. https://doi.org/10.1007/s10681-019-2440-3

Brouwer DJ, St Clair DA (2004) Fine mapping of three quantitative trait loci for late blight resistance in tomato using near isogenic lines (NILs) and sub-NILs. Theor Appl Genet 108:628–638. https://doi.org/10.1007/s00122-003-1469-8

Brouwer DJ, Jones ES, St Clair DA (2004) QTL analysis of quantitative resistance to *Phytophthora infestans* (late blight) in tomato and comparisons with potato. Genome 47(3):475–492. https://doi.org/10.1139/g04-001

Brun H, Chevre AM, Fitt BDL, Powers S, Besnard AL, Ermel M, Huteau V, Marquer B, Eber F, Renard M, Andrivon D (2010) Quantitative resistance increases the durability of qualitative resistance to *Leptosphaeria maculans* in *Brassica napus*. New Phytol 185:285–299. https://doi.org/10.1111/j.1469-8137.2009.03049.x

Cai Y, Yu X, Hu S, Yu J (2009) A brief review on the mechanisms of miRNA regulation. Genom Proteom Bioinf 7(4):147–154. https://doi.org/10.1016/S1672-0229(08)60044-3

Champouret N (2010) Functional genomics of *Phytophthora infestans* effectors and Solanum resistance genes. PhD Thesis, Wageningen University

Chauhan S, Yogindran S, Rajam MV (2017) Role of miRNAs in biotic stress reactions in plants. Indian J Plant Physiol 22(4):514–529. https://doi.org/10.1007/s40502-017-0347-3

Chen AL, Liu CY, Chen CH, Wang JF, Liao YC, Chang CH, Tsai MH, Hwu KK, Chen KY (2014) Reassessment of QTLs for late blight resistance in the tomato accession L3708 using a restriction site associated DNA (RAD) linkage map and highly aggressive isolates of *Phytophthora infestans*. PLoS ONE 9(5):e96417. https://doi.org/10.1371/journal.pone.0096417

Chen XR, Li YP, Li QY, Xing YP, Liu BB, Tong YH, Xu JY (2016) *SCR 96*, a small cysteine-rich secretory protein of *Phytophthora cactorum*, can trigger cell death in the Solanaceae and is important for pathogenicity and oxidative stress tolerance. Mol Plant Pathol 17:577–587. https://doi.org/10.1111/mpp.12303

Chen L, Meng J, Zhai J, Xu P, Luan Y (2017) MicroRNA396a-5p and-3p induce tomato disease susceptibility by suppressing target genes and upregulating salicylic acid. Plant Sci 265:177–187. https://doi.org/10.1016/j.plantsci.2017.10.004

Chen L, Meng J, He XL, Zhang M, Luan YS (2018) *Solanum lycopersicum* microRNA1916 targets multiple target genes and negatively regulates the immune response in tomato. Plant Cell Environ 42(4):1393–1407. https://doi.org/10.1111/pce.13468

Cheval C, Aldon D, Galaud JP, Ranty B (2013) Calcium/calmodulin-mediated regulation of plant immunity. BBA-Mol Cell Res 7:1766–1771. https://doi.org/10.1016/j.bbamcr.2013.01.031

Chinchilla D, Zipfel C, Robatzek S, Kemmerling B, Nürnberger T, Jones JD, Felix G, Boller T (2007) A flagellin-induced complex of the receptor FLS2 and BAK1 initiates plant defence. Nature 448(7152):497–500. https://doi.org/10.1038/nature05999

Chunwongse J, Chunwongse C, Black L, Hanson P (2002) Molecular mapping of the *Ph-3* gene for late blight resistance in tomato. J Hortic Sci Biotechnol 77:281–286. https://doi.org/10.1080/14620316.2002.11511493

Collard BC, Mackill DJ (2008) Marker-assisted selection: an approach for precision plant breeding in the twenty-first century. Philos T R Soc B 363(1491):557–572. https://doi.org/10.1098/rstb.2007.2170

Collard BCY, Jahufer MZZ, Brouwer JB, Pang ECK (2005) An introduction to markers, quantitative trait loci (QTL) mapping and marker-assisted selection for crop improvement: the basic concepts. Euphytica 142:169–196. https://doi.org/10.1007/s10681-005-1681-5

Cui J, Jiang N, Zhou X, Hou X, Yang G, Meng J, Luan Y (2018a) Tomato *MYB49* enhances resistance to *Phytophthora infestans* and tolerance to water deficit and salt stress. Planta 248(6):1487–1503. https://doi.org/10.1007/s00425-018-2987-6

Cui J, Xu P, Meng J, Li J, Jiang N, Luan Y (2018b) Transcriptome signatures of tomato leaf induced by *Phytophthora infestans* and functional identification of transcription factor *SpWRKY3*. Theor Appl Genet 131(4):787–800. https://doi.org/10.1007/s00122-017-3035-9

Cui J, Jiang N, Meng J, Yang G, Liu W, Zhou X, Ma N, Hou X, Luan Y (2019) LncRNA33732-respiratory burst oxidase module associated with WRKY1 in tomato-*Phytophthora infestans* interactions. Plant J 97(5):933–946. https://doi.org/10.1111/tpj.14173

Damasceno CM, Bishop JG, Ripoll DR, Win J, Kamoun S, Rose JK (2008) Structure of the glucanase inhibitor protein (GIP) family from *Phytophthora* species suggests coevolution with plant endo-β-1, 3-glucanases. Mol Plant-Microbe Interact 21(6):820–830. https://doi.org/10.1094/mpmi-21-6-0820

Dangl JL, Jones JD (2001) Plant pathogens and integrated defence responses to infection. Nature 411(6839):826–833. https://doi.org/10.1038/35081161

Danilo B, Perrot L, Mara K, Botton E, Nogué F, Mazier M (2019) Efficient and transgene-free gene targeting using *Agrobacterium*-mediated delivery of the CRISPR/Cas9 system in tomato. Plant Cell Rep 38(4):459–462. https://doi.org/10.1007/s00299-019-02373-6

Derevnina L, Dagdas YF, De la Concepcion JC, Bialas A, Kellner R, Petre B, Domazakis E, Du J, Wu CH, Lin X, Aguilera-Galvez C (2016) Nine things to know about elicitins. New Phytol 212(4):888–895. https://doi.org/10.1111/nph.14137

Drenth A, Janssen EM, Govers F (1995) Formation and survival of oospores of *Phytophthora infestans* under natural conditions. Plant Pathol 44:86–94. https://doi.org/10.1111/j.1365-3059.1995.tb02719.x

Du Y, Mpina MH, Birch PR, Bouwmeester K, Govers F (2015) *Phytophthora infestans* RXLR effector AVR1 interacts with exocyst component Sec5 to manipulate plant immunity. Plant Physiol 169(3):1975–1990. https://doi.org/10.1104/pp.15.01169

Elmore JM, Lin ZJ, Coaker G (2011) Plant NB-LRR signaling: upstream and downstream. Curr Opin Plant Biol 14:365–371. https://doi.org/10.1016/j.pbi.2011.03.011

Elsoud MM, Kady EMI (2019) Current trends in fungal biosynthesis of chitin and chitosan. Bull Natl Res Cent 43:59. https://doi.org/10.1186/s42269-019-0105-y

Erpen L, Devi HS, Grosser JW, Dutt M (2017) Potential use of the *DREB/ERF*, *MYB*, *NAC* and *WRKY* transcription factors to improve abiotic and biotic stress in transgenic plants. Plant Cell Tissue Organ Cult 32(1):1–25. https://doi.org/10.1007/s11240-017-1320-6

Erwin DC, Ribeiro OK (1996) *Phytophthora* Diseases worldwide. American Phytopathological Society, St Paul, p 562

Faino L, Carli P, Testa A, Cristinzio G, Frusciante L, Ercolano MR (2010) Potato *R1* resistance gene confers resistance against *Phytophthora infestans* in transgenic tomato plants. Eur J Plant Pathol 128(2):233–241. https://doi.org/10.1007/s10658-010-9649-2

Foolad MR, Panthee DR (2012) Marker-assisted selection in tomato breeding. Crit Rev Plant Sci 31:93–123. https://doi.org/10.1080/07352689.2011.616057

Foolad MR, Merk HL, Ashrafi H (2008) Genetics, genomics and breeding of late blight and early blight resistance in tomato. Crit Rev Plant Sci 27(2):75–107. https://doi.org/10.1080/07352680802147353

Fry W (2008) *Phytophthora infestans*: the plant (and *R* gene) destroyer. Mol Plant Pathol 9(3):385–402. https://doi.org/10.1111/j.1364-3703.2007.00465.x

Furuichi N, Yukokokawa K, Okamura H, Ohta M (2013) A novel elicitor (PiPE) from *Phytophthora infestans* induces active oxygen species and the hypersensitive response in potato. Glob J Med Res 8:1–14

Furuichi N, Yokokawa K, Okamura H, Ohta M (2014) PiPE, a Phytophthora-associated PAMPS from *P. infestans*, Binds to a Ca2+-dependent protein kinase (CDPK) in potato for the induction of hypersensitive reaction. J Clin Exp Pathol 4(156):2161–2681. https://doi.org/10.4172/2161-0681.1000156

Gallegly ME, Marvel ME (1955) Inheritance of resistance to tomato race-0 of *Phytophthora infestans*. J Phytopathol 45:103–109

Gardner RG, Panthee DR (2010) NC 1 CELBR and NC 2 CELBR: early blight and late blight resistant fresh market tomato breeding lines. HortScience 45:975–976. https://doi.org/10.21273/HORTSCI.45.6.975

Ghislain M, Trognitz B, Herrera MD, Solis J, Casallo G, Vasquez C, Hurtado O, Castillo R, Portal L, Orrillo M (2001) Genetic loci associated with field resistance to late blight in offspring

of *Solanum phureja* and *S. tuberosum* grown under short-day conditions. Theor Appl Genet 103(2–3):433–442

Ghorbani Faal P, Farsi M, Seifi A, Mirshamsi Kakhki A (2020) Virus-induced CRISPR-Cas9 system improved resistance against tomato yellow leaf curl virus. Mol Biol Rep 15:1–8. https://doi.org/10.1007/s11033-020-05409-3

Gilroy EM, Taylor RM, Hein I, Boevink P, Sadanandom A, Birch PR (2011) CMPG1-dependent cell death follows perception of diverse pathogen elicitors at the host plasma membrane and is suppressed by *Phytophthora infestans* RXLR effector AVR3a. New Phytol 190(3):653–666. https://doi.org/10.1111/j.1469-8137.2011.03643.x

Goodwin SB, Sujkowski LS, Fry WE (1995) Rapid evolution of pathogenicity within clonal lineages of the potato late blight disease Fungus. J Phytopathol 85:669–676. https://doi.org/10.1094/Phyto-85-669

Grund E, Tremousaygue D, Deslandes L (2019) Plant NLRs with integrated domains: unity makes strength. Plant Physiol 179(4):1227–1235. https://doi.org/10.1104/pp.18.01134

Guerriero G, Avino M, Zhou Q, Fugelstad J, Clergeot PH, Bulone V (2010) Chitin synthases from Saprolegnia are involved in tip growth and represent a potential target for anti-oomycete drugs. PLoS Pathog 26(8):1001070. https://doi.org/10.1371/journal.ppat.1001070

Haas BJ, Kamoun S, Zody MC, Rays Jiang RHY, Handsaker RE, Cano LM, Grabherr M, Kodira CD, Raffaele S, Torto-Alalibo T, Bozkurt TO, Ah-Fong AMV, Alvarado L, Anderson VL, Armstrong MR, Avrova A, Baxter L, Beynon J, Boevink PC, Bollmann SR, Bos JIB, Bulone V, Cai G, Cakir C, Carrington JC, Chawner M, Conti L, Costanzo S, Ewan R, Fahlgren N, Fischbach MA, Fugelstad J, Gilroy EM, Gnerre S, Green PJ, Grenville-Briggs LJ, Griffith J, Grünwald NJ, Horn K, Horner NR, Hu C-H, Huitema E, Jeong D-H, Jones AME, Jones JDG, Jones RW, Karlsson EK, Kunjeti SG, Lamour K, Liu Z, Ma L, Maclean D, Chibucos MC, McDonald H, McWalters J, Meijer HJG, Morgan W, Morris PF, Munro CA, O'Neill K, Ospina-Giraldo M, Pinzón A, Pritchard L, Ramsahoye B, Ren Q, Restrepo S, Roy S, Sadanandom A, Savidor A, Schornack S, Schwartz DC, Schumann UD, Schwessinger B, Seyer L, Sharpe T, Silvar C, Song J, Studholme DJ, Sykes S, Thines M, Vondervoort PJIV, Phuntumart V, Wawra S, Weide R, Win J, Young C, Zhou S, Fry W, Meyers BC, West PV, Ristaino J, Govers F, Birch PRJ, Whisson SC, Judelson HS, Nusbaum C (2009) Genome sequence and analysis of the Irish potato famine pathogen *Phytophthora infestans*. Nature 461:393–398. https://doi.org/10.1038/nature08358

Haggard JE, Johnson EB, Clair DA (2015) Multiple QTL for horticultural traits and quantitative resistance to *Phytophthora infestans* linked on *Solanum habrochaites* chromosome 11. G3: Genes, Genomes, Genetics 5(2):219–233. https://doi.org/10.1534/g3.114.014654

Hinkel L, Ospina-Giraldo MD (2017) Structural characterization of a putative chitin synthase gene in *Phytophthora* spp and analysis of its transcriptional activity during pathogenesis on potato and soybean plants. Curr Genet 63(5):909–921. https://doi.org/10.1007/s00294-017-0687-6

Hong Y, Cui J, Liu Z, Luan Y (2018) *SpWRKY6* acts as a positive regulator during tomato resistance to *Phytophthora infestans* infection. Biochem Biophys Res Commun 506(4):787–792. https://doi.org/10.1016/j.bbrc.2018.10.155

Hong YH, Meng J, He XL, Zhang YY, Luan YS (2019) Overexpression of *MiR482c* in tomato induces enhanced susceptibility to late blight. Cells 8(8):822. https://doi.org/10.3390/cells8080822

Hong YH, Meng J, Zhang M, Luan YS (2020) Identification of tomato circular RNAs responsive to *Phytophthora infestans*. Gene 4:144652. https://doi.org/10.1016/j.gene.2020.144652

Hoshikawa K, Fujita S, Renhu N, Ezura K, Yamamoto T, Nonaka S, Ezura H, Miura K (2019) Efficient transient protein expression in tomato cultivars and wild species using agroinfiltration-mediated high expression system. Plant Cell Rep 38(1):75–84. https://doi.org/10.1007/s00299-018-2350-1

Huang J, Chen L, Lu X, Peng Q, Zhang Y, Yang J, Zhang BY, Yang B, Waletich JR, Yin W, Zheng X (2019) Natural allelic variations provide insights into host adaptation of *Phytophthora* avirulence effector *PsAvr3c*. New Phytol 221(2):1010–1022. https://doi.org/10.1038/s41467-017-02233-5

Huet JC, Salle-Tourne M, Pernollet JC (1994) Amino acid sequence and toxicity of the alpha elicitin secreted with ubiquitin by *Phytophthora infestans*. Mol Plant Microbe Interact 7(2):302–304. https://doi.org/10.1094/MPMI-7-0302

Jain D, Khurana JP (2018) Role of pathogenesis-related (PR) proteins in plant defense mechanism. In: Singh A, Singh IK (eds) Molecular aspects of plant-pathogen interaction. Springer, Singapore, pp 265–281

Jelenska J, Davern SM, Standaert RF, Mirzadeh S, Greenberg JT (2017) Flagellin peptide flg22 gains access to long-distance trafficking in *Arabidopsis* via its receptor, FLS2. J Exp Bot 68(7):1769–1783. https://doi.org/10.1093/jxb/erx060

Jiang RH, Tripathy S, Govers F, Tyler BM (2008) RXLR effector reservoir in two *Phytophthora* species is dominated by a single rapidly evolving superfamily with more than 700 members. Proc Natl Acad Sci USA 105:4874–4879. https://doi.org/10.1073/pnas.0709303105

Jiang N, Cui J, Meng J, Luan Y (2018a) A tomato nucleotide binding sites− leucine-rich repeat gene is positively involved in plant resistance to *Phytophthora infestans*. Phytopathol 108(8):980–987. https://doi.org/10.1094/PHYTO-12-17-0389-R

Jiang N, Meng J, Cui J, Sun G, Luan Y (2018b) Function identification of miR482b, a negative regulator during tomato resistance to *Phytophthora infestans*. Hortic Res 5(1):1–1. https://doi.org/10.1038/s41438-018-0017-2

Jiang N, Cui J, Hou X, Yang G, Xiao Y, Han L, Meng J, Luan Y (2020) Sl-lncRNA15492 interacts with Sl-miR482a and affects *Solanum lycopersicum* immunity against *Phytophthora infestans*. Plant J 103(4):1561–1574. https://doi.org/10.1111/tpj.14847

Johnson EB, Haggard JE, Clair DA (2012) Fractionation, stability, and isolate-specificity of QTL for resistance to *Phytophthora infestans* in cultivated tomato (*Solanum lycopersicum*). G3: Genes, Genomes, Genetics 2(10):1145–1159. https://doi.org/10.1534/g3.112.003459

Jones JDG, Dangl JL (2006) The plant immune system. Nature 444:323. https://doi.org/10.1038/nature05286

Judelson HS (2007) Sexual reproduction in plant pathogenic oomycetes: biology and impact on disease. In: Heitman J, Kronstad JW, Taylor JW, Casselton LA (eds) Sex in fungi: molecular determinationand evolutionary implications. ASM Press, pp 445–458

Judelson HS, Tani S, Narayan RD (2009) Metabolic adaptation of *Phytophthora infestans* during growth on leaves, tubers and artificial media. Mol Plant Pathol 10(6):843–855. https://doi.org/10.1111/j.1364-3703.2009.00570.x

Kamoun S, Furzer O, Jones JD, Judelson HS, Ali GS, Dalio RJ, Roy SG, Schena L, Zambounis A, Panabières F, Cahill D, Ruocco M, Figueiredo A, Chen XR, Hulvey J, Stam R, Lamour K, Gijzen M, Tyler BM, Grünwald NJ, Mukhtar MS, Tomé DF, Tör M, Van Den Ackerveken G, McDowell J, Daayf F, Fry WE, Lindqvist-Kreuze H, Meijer HJ, Petre B, Ristaino J, Yoshida K, Birch PR, Govers F (2015) The Top 10 oomycete pathogens in molecular plant pathology. Mol Plant Pathol 16:413–434. https://doi.org/10.1111/mpp.12190

Kanneganti TD, Huitema E, Cakir C, Kamoun S (2006) Synergistic interactions of the plant cell death pathways induced by *Phytophthora infestans* Nep1-like protein PiNPP1. 1 and INF1

elicitin. Mol Plant Microbe Interact 19(8):854–863. https://doi.org/10.1094/MPMI-19-0854

Kawamura Y, Hase S, Takenaka S, Kanayama Y, Yoshioka H, Kamoun S, Takahashi H (2009) INF1 elicitin activates jasmonic acid-and ethylene-mediated signalling pathways and induces resistance to bacterial wilt disease in tomato. J Phytopathol 157(5):287–297. https://doi.org/10.1111/j.1439-0434.2008.01489.x

Keizer DW, Schuster B, Grant BR, Gayler KR (1998) Interactions between elicitins and radish *Raphanus sativus*. Planta 204(4):480–489. https://doi.org/10.1007/s004250050282

Khaliluev MR, Mamonov AG, Smirnov AN, Kharchenko PN, Dolgov SV (2011) Expression of genes encoding chitin-binding proteins (*PR-4*) and hevein-like antimicrobial peptides in transgenic tomato plants enhanced resistanse to *Phytophthora infestance*. Russ Agric Sci 37(4):297. https://doi.org/10.3103/S1068367411040082

King SR, McLellan H, Boevink PC, Armstrong MR, Bukharova T, Sukarta O, Win J, Kamoun S, Birch PR, Banfield MJ (2014) *Phytophthora infestans* RXLR effector *PexRD2* interacts with host MAPKKKε to suppress plant immune signalling. Plant Cell 26(3):1345–1359. https://doi.org/10.1105/tpc.113.120055

Koeck M, Hardham AR, Dodds PN (2011) The role of effectors of biotrophic and hemibiotrophic fungi in infection. Cell Microbiol 13(12):1849–1857. https://doi.org/10.1111/j.1462-5822.2011.01665.x

Kole C, Ashrafi H, Lin G, Foolad M (2006) Identification and molecular mapping of a new R gene, Ph-4, conferring resistance to late blight in tomato. Proceedings of Solanaceae Conference; University of Wisconsin, Madison, Abstract 449

Korneeva IV, Varlamova NV, Pushin AS, Firsov AP, Dolgov SV, Monakhos GF, Motamedi SA, Dzhalilov FS, Korneeva IV, Varlamova NV (2010) Transgenic tomato plants expressing PR-5 protein genes demonstrated disease resistance against *Phytophthora infestans* and *Xanthomonas vesicatoria*. Acta Hortic 914:415–418. https://doi.org/10.17660/ActaHortic.2011.914.79

Kots K, Meijer HJ, Bouwmeester K, Govers F, Ketelaar T (2017) Filamentous actin accumulates during plant cell penetration and cell wall plug formation in *Phytophthora infestans*. Cell Mole Life Sci 74(5):909–920. https://doi.org/10.1007/s00018-016-2383-y

Kung JT, Colognori D, Lee JT (2013) Long noncoding RNAs: past, present, and future. Genetics 193(3):651–669. https://doi.org/10.1534/genetics.112.146704

Leesutthiphonchai W, Vu AL, Ah-Fong AMV, Judelson HS (2018) How does *Phytophthora infestans* evade control efforts? Modern insight into the late blight disease. Phytopathol 108:916–924. https://doi.org/10.1094/PHYTO-04-18-0130-IA

Li B (2008) Reasons of late blight affecting processing tomato in Baynnur in 2007. China Veg 8:59–60 ((**in Chinese**))

Li J, Liu L, Bai Y, Finkers R, Wang F, Du Y, Yang Y, Xie B, Visser RG, van Heusden AW (2011) Identification and mapping of quantitative resistance to late blight (*Phytophthora infestans*) in *Solanum habrochaites* LA1777. Euphytica 179(3):427–438. https://doi.org/10.1007/s10681-010-0340-7

Li JB, Luan YS, Liu Z (2015) *SpWRKY1* mediates resistance to *Phytophthora infestans* and tolerance to salt and drought stress by modulating reactive oxygen species homeostasis and expression of defense-related genes in tomato. Plant Cell Tissue Organ Cult 123(1):67–81. https://doi.org/10.1007/s11240-015-0815-2

Liu Z, Bos JI, Armstrong M, Whisson SC, da Cunha L, Torto-Alalibo T, Win J, Avrova AO, Wright F, Birch PR, Kamoun S (2005) Patterns of diversifying selection in the phytotoxin-like scr74 gene family of *Phytophthora infestans*. Mol Biol Evol 22(3):659–672. https://doi.org/10.1093/molbev/msi049

Lobo M, Navarro R (1987) Late blight horizontal resistance in *L. esculentum* × *L. hirsutum* hybrids. Rep Tomato Genet Coop 37:53

Luan Y, Cui J, Wang W, Meng J (2016) MiR1918 enhances tomato sensitivity to *Phytophthora infestans* infection. Sci Rep 6:35858. https://doi.org/10.1038/srep35858

Luan Y, Cui J, Li J, Jiang N, Liu P, Meng J (2018) Effective enhancement of resistance to *Phytophthora infestans* by overexpression of miR172a and b in *Solanum lycopersicum*. Planta 247(1):127–138. https://doi.org/10.1007/s00425-017-2773-x

Ma NN, Zuo YQ, Liang XQ, Yin B, Wang GD, Meng QW (2013) The multiple stress-responsive transcription factor *SlNAC1* improves the chilling tolerance of tomato. Physiol Plant 149:474–486. https://doi.org/10.1111/ppl.12049

Maffei ME, Arimura GI, Mithöfer A (2012) Natural elicitors, effectors and modulators of plant responses. Natural Prod Rep 29(11):1288–1303. https://doi.org/10.1039/c2np20053h

Malik NAA, Kumar IS, Nadarajah K (2020) Elicitor and receptor molecules: orchestrators of plant defense and immunity. Int J Mol Sci 21(3):963. https://doi.org/10.3390/ijms21030963

McLellan H, Boevink PC, Armstrong MR, Pritchard L, Gomez S, Morales J, Whisson SC, Beynon JL, Birch PR (2013) An RxLR effector from *Phytophthora infestans* prevents re-localisation of two plant NAC transcription factors from the endoplasmic reticulum to the nucleus. PLoS Pathog 9(10):1003670. https://doi.org/10.1371/journal.ppat.1003670

Merk HL, Ashrafi H, Foolad MR (2012) Selective genotyping to identify late blight resistance genes in an accession of the tomato wild species *Solanum pimpinellifolium*. Euphytica 187(1):63–75. https://doi.org/10.1007/s10681-012-0729-6

Murphy F, He Q, Armstrong M, Giuliani LM, Boevink PC, Zhang W, Tian Z, Birch PR, Gilroy EM (2018) The potato MAP3K StVIK is required for the *Phytophthora infestans* RXLR effector Pi17316 to promote disease. Plant Physiol 177(1):398–410. https://doi.org/10.1104/pp.18.00028

Noman A, Aqeel M, Irshad MK, Qari SH, Hashem M, Alamri S, Abdul Majeed AM, Al-Sadi AM (2020) Elicitins as molecular weapons against pathogens: consolidated biotechnological strategy for enhancing plant growth. Crit Rev Biotechnol. https://doi.org/10.1080/07388551.2020.1779174

Nowicki M, Foolad MR, Nowakowska M, Kozik EU (2012) Potato and tomato late blight caused by *Phytophthora infestans*: an overview of pathology and resistance breeding. Plant Dis 96(1):4–17. https://doi.org/10.1094/PDIS-05-11-0458

Ohlson EW, Ashrafi H, Foolad MR (2018) Identification and mapping of late blight resistance quantitative trait loci in tomato accession PI 163245. Plant Genome 11(3):1–6. https://doi.org/10.1007/10.3835/plantgenome2018.01.0007

Ospina-Giraldo MD, Griffith JG, Laird EW, Mingora C (2010) The CAZyome of *Phytophthora* spp.: a comprehensive analysis of the gene complement coding for carbohydrate-active enzymes in species of the genus Phytophthora. BMC Genomics 11(1):525. https://doi.org/10.1186/1471-2164-11-525

Ottmann C, Luberacki B, Küfner I, Koch W, Brunner F, Weyand M, Mattinen L, Pirhonen M, Anderluh G, Seitz HU, Nürnberger T (2009) A common toxin fold mediates microbial attack and plant defense. Proc Natl Acad Sci USA 106(25):10359–10364. https://doi.org/10.1073/pnas.0902362106

Pandey SP, Somssich IE (2009) The role of WRKY transcription factors in plant immunity. Plant Physiol 150(4):1648–1655. https://doi.org/10.1104/pp.109.138990

Panstruga R, Dodds PN (2009) Terrific protein traffic: the mystery of effector protein delivery by filamentous plant pathogens. Sci 324:748–750. https://doi.org/10.1126/science.1171652

Panthee DR, Gardner RG (2010) 'Mountain Merit': a late blight resistant large-fruited tomato hybrid. HortScience 45:1547–1548. https://doi.org/10.21273/HORTSCI.45.10.1547

Panthee DR, Piotrowski A, Ibrahem R (2017) Mapping quantitative trait loci (QTL) for resistance to Late Blight in tomato. Int J Mol Sci 18(7):1589. https://doi.org/10.3390/ijms18071589

Parage C, Tavares R, Réty S, Baltenweck-Guyot R, Poutaraud A, Renault L, Heintz D, Lugan R, Marais GA, Aubourg S, Hugueney P (2012) Structural, functional, and evolutionary analysis of the unusually large *stilbene synthase* gene family in grapevine. Plant Physiol 160(3):1407–1419. https://doi.org/10.1104/pp.112.202705

Peirce LC (1971) Linkage tests with *Ph* conditioning resistance to race 0 *Phytophthora infestans*. Tomato Genet Coop Rep 21:30

Pel MA, Foster SJ, Park T-H, Rietman H, Gv A, Jones JDG, Eck HJV, Jacobsen E, Visser RGF, Vossen EAGV (2009) Mapping and cloning of late blight resistance genes from *Solanum venturii* using an interspecific candidate gene approach. Mol Plant Microbe Interact 22:601–615. https://doi.org/10.1094/MPMI-22-5-0601

Petit-Houdenot Y, Fudal I (2017) Complex interactions between fungal avirulence genes and their corresponding plant resistance genes and consequences for disease resistance management. Front Plant Sci 16(8):1072. https://doi.org/10.3389/fpls.2017.01072

Pitzschke A, Schikora A, Hirt H (2009) MAPK cascade signalling networks in plant defence. Curr Opin Plant Biol 12(4):421–426. https://doi.org/10.1016/j.pbi.2009.06.008

Poudel A, Pandey M, Shah K, Acharya B, Shrestha J (2020) Evaluation of fungicides for management of late blight (*Phytophthora infestans*) of potato. Agrica 9(1):10–17. https://doi.org/10.5958/2394-448X.2020.00004.8

Qi D, Innes RW (2013) Recent advances in plant NLR structure, function, localization, and signaling. Front Immunol 4:348. https://doi.org/10.3389/fimmu.2013.00348

Qutob D, Kemmerling B, Brunner F, Küfner I, Engelhardt S, Gust AA, Luberacki B, Seitz HU, Stahl D, Rauhut T, Glawischnig E (2006) Phytotoxicity and innate immune responses induced by Nep1-like proteins. Plant Cell 18(12):3721–3744. https://doi.org/10.1105/tpc.106.044180

Raffaele S, Farrer RA, Cano LM, Studholme DJ, MacLean D, Thines M, Jiang RH, Zody MC, Kunjeti SG, Donofrio NM, Meyers BC (2010) Genome evolution following host jumps in the Irish potato famine pathogen lineage. Sci 330(6010):1540–1543. https://doi.org/10.1126/science.1193070

Ratti M, Lampis A, Ghidini M, Salati M, Mirchev MB, Valeri N, Hahne JC (2020) MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) as new tools for cancer therapy: first steps from bench to bedside. Target Oncol 15(3):261–278. https://doi.org/10.1007/s11523-020-00717-x

Ren Y, Armstrong M, Qi Y, McLellan H, Zhong C, Du B, Birch PR, Tian Z (2019) *Phytophthora infestans* RXLR effectors target parallel steps in an immune signal transduction pathway. Plant Physiol 180(4):2227–2239. https://doi.org/10.1104/pp.18.00625

Ricci P, Bonnet P, Huet JC, Sallantin M, Beauvais-cante F, Bruneteau M, Billard V, Michel G, Pernollet JC (1989) Structure and activity of proteins from pathogenic fungi *Phytophthora* eliciting necrosis and acquired resistance in tobacco. Eur J Biochem 183(3):555–563. https://doi.org/10.1111/j.1432-1033.1989.tb21084.x

Rodenburg SY, Seidl MF, De Ridder D, Govers F (2018) Genome-wide characterization of *Phytophthora infestans* metabolism: a systems biology approach. Mol Plant Pathol 19(6):1403–1413. https://doi.org/10.1111/mpp.12623

Rodenburg SY, Seidl MF, Judelson HS, Vu AL, Govers F, de Ridder D (2019) Metabolic model of the *Phytophthora infestans*-tomato interaction reveals metabolic switches during host colonization. Mbio 10(4):e00454-e519. https://doi.org/10.1128/mBio.00454-19

Rodewald J, Trognitz B (2013) Solanum resistance genes against *Phytophthora infestans* and their corresponding avirulence genes. Mol Plant Pathol 14(7):740–757. https://doi.org/10.1111/mpp.12036

Saunders DGO, Win J, Cano LM, Szabo LJ, Kamoun S, Raffaele S (2012a) Using hierarchical clustering of secreted protein families to classify and rank candidate effectors of rust fungi. PLoS ONE 7:e29847. https://doi.org/10.1371/journal.pone.0029847

Saunders DG, Breen S, Win J, Schornack S, Hein I, Bozkurt TO, Champouret N, Vleeshouwers VG, Birch PR, Gilroy EM, Kamoun S (2012b) Host protein BSL1 associates with *Phytophthora infestans* RXLR effector AVR2 and the *Solanum demissum* immune receptor R2 to mediate disease resistance. Plant Cell 24(8):3420–3434. https://doi.org/10.1105/tpc.112.099861

Schornack S, van Damme M, Bozkurt TO, Cano LM, Smoker M, Thines M, Gaulin E, Kamoun S, Huitema E (2010) Ancient class of translocated oomycete effectors targets the host nucleus. Proc Natl Acad Sci USA 107(40):17421–17426. https://doi.org/10.1073/pnas.1008491107

Schultz D, Donahoo RS, Perez FG, Tejeda S, Roberts PD, Deahl K (2010) A survey of tomato and potato fields in Florida reveals unique genotypes of *Phytophthora infestans* between 2005 and 2007. HortScience 45(7):1064–1068. https://doi.org/10.21273/HORTSCI.45.7.1064

Seifu YW (2017) Reducing severity of late blight (*Phytophthora infestans*) and improving potato (*Solanum tuberosum* L.) tuber yield with pre-harvest application of calcium nutrients. Agronomy 7(4):69. https://doi.org/10.3390/agronomy7040069

Senchou V, Weide R, Carrasco A, Bouyssou H, Pont-Lezica R, Govers F, Canut H (2004) High affinity recognition of a *Phytophthora* protein by Arabidopsis via an RGD motif. Cell Mol Life Sci 61(4):502–509. https://doi.org/10.1007/s00018-003-3394-z

Shah SR, Tao L, Haijuan C, Lei L, Zheng Z, Junming L, Yongchen D (2014) Age-related resistance and the defense signalling pathway of *Ph-3* gene against *Phytophthora infestans* in tomatoes. Hortic Plant J 1(2):70–76. https://doi.org/10.16420/j.issn.2095-9885.2015-0019

Sharpee WC, Dean RA (2016) Form and function of fungal and oomycete effectors. Fungal Biol Rev 30(2):62–73. https://doi.org/10.1016/j.fbr.2016.04.001

Smart CD, Tanksley SD, Mayton H, Fry WE (2007) Resistance to *Phytophthora infestans* in *Lycopersicon pennellii*. Plant Dis 91(8):1045–1049. https://doi.org/10.1094/PDIS-91-8-1045

Song J, Win J, Tian M, Schornack S, Kaschani F, Ilyas M, van der Hoorn RA, Kamoun S (2009) Apoplastic effectors secreted by two unrelated eukaryotic plant pathogens target the tomato defense protease Rcr3. Proc Natl Acad Sci USA 106:1654–1659. https://doi.org/10.1073/pnas.0809201106

Sun K, Wolters AM, Loonen AE, Huibers RP, van der Vlugt R, Goverse A, Jacobsen E, Visser RG, Bai Y (2016) Down-regulation of Arabidopsis *DND1* orthologs in potato and tomato leads to broad-spectrum resistance to late blight and powdery mildew. Transgenic Res 25(2):123–138. https://doi.org/10.1007/s11248-015-9921-5

Takken FL, Goverse A (2012) How to build a pathogen detector: structural basis of NB-LRR function. Curr Opin Plant Biol 15:375–384. https://doi.org/10.1016/j.pbi.2012.05.001

Takken FL, Albrecht M, Tameling WI (2006) Resistance proteins: molecular switches of plant defence. Curr Opin Plant Biol 9(4):383–390. https://doi.org/10.1016/j.pbi.2006.05.009

Thomzik JE, Stenzel K, Stöcker R, Schreier PH, Hain R, Stahl DJ (1997) Synthesis of a grapevine phytoalexin in transgenic tomatoes (*Lycopersicon esculentum* Mill.) conditions resistance against *Phytophthora infestans*. Physiol Mol Plant Pathol 51(4):265–278. https://doi.org/10.1007/BF03543002

Tian M, Huitema E, da Cunha L, Torto-Alalibo T, Kamoun S (2004) A Kazal-like extracellular serine protease inhibitor from *Phytophthora infestans* targets the tomato pathogenesis-related protease P69B. J Biol Chem 279(25):26370–26377. https://doi.org/10.1074/jbc.M400941200

Tian Z, He Q, Wang H, Liu Y, Zhang Y, Shao F, Xie C (2015) The potato ERF transcription factor StERF3 negatively regulates resistance to *Phytophthora infestans* and salt tolerance in potato. Plant Cell Physiol 56(5):992–1005. https://doi.org/10.1093/pcp/pcv025

Torto TA, Li S, Styer A, Huitema E, Testa A, Gow NA, Van West P, Kamoun S (2003) EST mining and functional expression assays identify extracellular effector proteins from the plant pathogen *Phytophthora*. Genome Res 13(7):1675–1685. https://doi.org/10.1101/gr.910003

Toruño TY, Stergiopoulos I, Coaker G (2016) Plant-pathogen effectors: cellular probes interfering with plant defenses in spatial and temporal manners. Annu Rev Phytopathol 54:419–441. https://doi.org/10.1146/annurev-phyto-080615-100204

Van der Biezen EA, Jones JD (1998) Plant disease-resistance proteins and the gene-for-gene concept. Trends Biochem Sci 23(12):454–456. https://doi.org/10.1016/s0968-0004(98)01311-5

Van der Hoorn RA, Kamoun S (2008) From guard to decoy: a new model for perception of plant pathogen effectors. Plant Cell 20(8):2009–2017. https://doi.org/10.1105/tpc.108.060194

Van der Vossen E, Sikkema A, Hekkert BT, Gros J, Stevens P, Muskens M, Wouters D, Pereira A, Stiekema W, Allefs S (2003) An ancient *R* gene from the wild potato species *Solanum bulbocastanum* confers broad-spectrum resistance to *Phytophthora infestans* in cultivated potato and tomato. Plant J 36(6):867–882. https://doi.org/10.1046/j.1365-313x.2003.01934.x

Van Schie CC, Takken FL (2014) Susceptibility genes 101: how to be a good host. Annu Rev Phytopathol 52:551–581. https://doi.org/10.1146/annurev-phyto-102313-045854

Vleeshouwers VG, Raffaele S, Vossen JH, Champouret N, Oliva R, Segretin ME, Rietman H, Cano LM, Lokossou A, Kessel G, Pel MA (2011) Understanding and exploiting late blight resistance in the age of effectors. Annu Rev Phytopathol 49:507–531. https://doi.org/10.1146/annurev-phyto-072910-095326

Wang W, Jiao F (2019) Effectors of *Phytophthora* pathogens are powerful weapons for manipulating host immunity. Planta 26:1–3. https://doi.org/10.1007/s00425-019-03219-x

Wang X, Boevink P, McLellan H, Armstrong M, Bukharova T, Qin Z, Birch PR (2015) A host KH RNA-binding protein is a susceptibility factor targeted by an RXLR effector to promote late blight disease. Mol Plant 8(9):1385–1395. https://doi.org/10.1016/j.molp.2015.04.012

Wang S, Boevink PC, Welsh L, Zhang R, Whisson SC, Birch PR (2017) Delivery of cytoplasmic and apoplastic effectors from *Phytophthora infestans* haustoria by distinct secretion pathways. New Phytol 216(1):205–215. https://doi.org/10.1111/nph.14696

Wawra S, Belmonte R, Löbach L, Saraiva M, Willems A, van West P (2012) Secretion, delivery and function of oomycete effector proteins. Curr Opin Microbiol 15(6):685–691. https://doi.org/10.1016/j.mib.2012.10.008

Wawra S, Trusch F, Matena A, Apostolakis K, Linne U, Zhukov I, Stanek J, Koźmiński W, Davidson I, Secombes CJ, Bayer P (2017) The RxLR motif of the host targeting effector AVR3a of *Phytophthora infestans* is cleaved before secretion. Plant Cell 29(6):1184–1195. https://doi.org/10.1105/tpc.16.00552

Wei C, Chen J, Kuang H (2016) Dramatic number variation of *R* genes in Solanaceae species accounted for by a few *R* gene subfamilies. PLoS ONE 11(2):e0148708. https://doi.org/10.1371/journal.pone.0148708

Win J, Krasileva KV, Kamoun S, Shirasu K, Staskawicz BJ, Banfield MJ (2012) Sequence divergent RXLR effectors share a structural fold conserved across plant pathogenic oomycete species. PLoS Pathog 8(1):1002400. https://doi.org/10.1371/journal.ppat.1002400

Yu CY, Kuo HC (2019) The emerging roles and functions of circular RNAs and their generation. J Biomed Sci 26(1):29. https://doi.org/10.1186/s12929-019-0523-z

Yuan H, Cheung CM, Poolman MG, Hilbers PA, van Riel NA (2016) A genome-scale metabolic network reconstruction of tomato (*Solanum lycopersicum* L.) and its application to photorespiratory metabolism. Plant J 85(2):289–304. https://doi.org/10.1111/tpj.13075

Zhang C, Liu L, Zheng Z, Sun Y, Zhou L, Yang Y, Cheng F, Zhang Z, Wang X, Huang S, Xie B (2013) Fine mapping of the *Ph-3* gene conferring resistance to late blight (*Phytophthora infestans*) in tomato. Theor Appl Genet 126(10):2643–2653. https://doi.org/10.1007/s00122-013-2162-1

Zhang C, Liu L, Wang X, Vossen J, Li G, Li T, Zheng Z, Gao J, Guo Y, Visser RG, Li J (2014) The *Ph-3* gene from *Solanum pimpinellifolium* encodes CC-NBS-LRR protein conferring resistance to *Phytophthora infestans*. Theor Appl Genet 127(6):1353–1364. https://doi.org/10.1007/s00122-014-2303-1

Zhang D, Burroughs AM, Vidal ND, Iyer LM, Aravind L (2016) Transposons to toxins: the provenance, architecture and diversification of a widespread class of eukaryotic effectors. Nucleic Acids Res 44(8):3513–3533. https://doi.org/10.1093/nar/gkw221

Zheng X, McLellan H, Fraiture M, Liu X, Boevink PC, Gilroy EM, Chen Y, Kandel K, Sessa G, Birch PR, Brunner F (2014) Functionally redundant RXLR effectors from *Phytophthora infestans* act at different steps to suppress early flg22-triggered immunity. PLoS Pathog 10(4):e1004057. https://doi.org/10.1371/journal.ppat.1004057

Zhou XT, Jia LJ, Wang HY, Zhao P, Wang WY, Liu N, Song SW, Wu Y, Su L, Zhang J, Zhong NQ (2018) The potato transcription factor *Stb ZIP 61* regulates dynamic biosynthesis of salicylic acid in defense against *Phytophthora infestans* infection. Plant J 95(6):1055–1068. https://doi.org/10.1111/tpj.14010

Zipfel C (2014) Plant pattern-recognition receptors. Trends Immunol 35(7):345–351. https://doi.org/10.1016/j.it.2014.05.004

Zuluaga AP, Vega-Arreguín JC, Fei Z, Ponnala L, Lee SJ, Matas AJ, Patev S, Fry WE, Rose JK (2016) Transcriptional dynamics of *Phytophthora infestans* during sequential stages of hemibiotrophic infection of tomato. Mol Plant Pathol 17(1):29–41. https://doi.org/10.1111/mpp.12263