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Early molecular events in the interaction between *Magnaporthe oryzae* and rice

Haifeng Zhang[1†], Jun Yang[2†], Muxing Liu[1†], Xiaozhou Xu[2], Leiyun Yang[1], Xinyu Liu[1], Youliang Peng[2*] and Zhengguang Zhang[1*]

Abstract

Rice is a staple crop feeding more than 50% of the world's population and, its sustainable production is crucial to the global food security. However, blast disease caused by the filamentous fungus *Magnaporthe oryzae* (anamorph: *Pyricularia oryzae*) threatens sustainable rice production as it can reduce grain yields over 30% in epidemic years. Therefore, deciphering the molecular mechanisms of the *M. oryzae*-rice interaction and the mechanism that how *M. oryzae* overcomes rice defense is crucial for developing new strategies to make green fungicides and disease-resistant rice varieties. This review provides a comprehensive overview of the latest advances in understanding the molecular mechanisms by which *M. oryzae* perceives host surface signals and subsequently develops specific infection structure called appressoria. In addition, the review delves into the strategies that the fungus utilizes to overcome host immunity, which in turn allows it to colonize rice tissues. Finally, we propose the perspectives for dissecting the pathogenesis of the fungus and controlling rice blast disease.

Keywords *Maganporthe oryzae*, Appressorium formation, Effector, Pathogenic mechanism, Disease control

Background

Rice is the most important staple food for over half of the global population (Elert 2014). However, rice production is threatened by blast disease, a devastating fungal disease caused by the ascomycetous filamentous fungus *Magnaporthe oryzae*. In China, the disease causes an annual loss over two million metric tons in rice yield, while the global yield loss caused by this disease can feed about 60 million people (Talbot 2003; Pennisi 2010; Zhang et al. 2016a). Although significant strides have been made to decipher the molecular mechanisms underlying the *M. oryzae*-rice interactions, blast disease remains a major threat to global rice production. Moreover, *M. oryzae* can infect other cereal crops, like wheat, barley, and millet, making it be a considerable economic concern (Inoue et al. 2017; Zhang et al. 2022b). Due to its economic importance and the availability of genetic manipulation for rice and *M. oryzae*, rice blast pathosystem has been widely used as a model system to investigate the molecular mechanisms underlying plant-pathogen interactions. This review focuses on recent advances in the molecular mechanisms of *M. oryzae* appressorium formation and the interaction between *M. oryzae* and rice. It discusses the molecular basis for developing effective and environmentally friendly fungicides and new strategies for blast-resistance rice breeding.

†Haifeng Zhang, Jun Yang and Muxing Liu have contributed equally.

*Correspondence:
Youliang Peng
pengyl@cau.edu.cn
Zhengguang Zhang
zhgzhang@njau.edu.cn
[1] Department of Plant Pathology, College of Plant Protection, Nanjing Agricultural University, and Key Laboratory of Integrated Management of Crop Diseases and Pests, Ministry of Education, Nanjing 210095, China
[2] MOA Key Laboratory for Monitoring and Green Management of Crop Pests, College of Plant Protection, China Agricultural University, Beijing 100193, China

Host surface recognition and functional appressorium formation

Host surface recognition and penetration are among the most critical steps during infection of foliar pathogens (Liu et al. 2011). Transmembrane proteins localized in the fungal cell membrane play essential roles in mediating surface recognition. During apical differentiation of germ tubes, *M. oryzae* conidia sense host physical cues, such as surface hardness and hydrophobicity by transmembrane receptor proteins, including Pth11 and MoSho1 (DeZwaan et al. 1999; Liu et al. 2011). Pth11 is an atypical heterotrimeric G-protein-coupled receptor (GPCR) with seven transmembrane regions and a common fungal extracellular membrane protein (CFEM) domain (Kulkarni et al. 2005; Ramanujam et al. 2013). The intracellular domain of Pth11 binds to a G protein and activates the cAMP signaling pathway (DeZwaan et al. 1999; Li et al. 2012). G proteins in *M. oryzae* are a heterotrimer, composing of a Gα subunit (MagA, MagB, and MagC), a Gβ subunit Mgb1, and a Gγ subunit Mgg1. Of these subunits, MagB, Mgb1, and Mgg1 are required for appressorium formation (Liu and Dean 1997; Nishimura et al. 2003; Li et al. 2015). Upon sensing physical cues, Pth11 undergoes a conformational change and acts as a guanylate exchange factor (GEF) to disassemble the G protein heterotrimer into a Gα subunit and a dimer of G$\beta\gamma$ by replacing the GDP with GTP on the G protein. This replacement results in the formation of Gα-GTP, an active state of G proteins, which activates the downstream cAMP-PKA signaling pathway; however, the released G$\beta\gamma$ initiates downstream signaling pathways, such as mitogen-activated protein kinase (MAPK) pathway, and ultimately, host physical cues are transduced to intracellular signals to induce functional appressorium formation (Hamel et al. 2012).

The activated Gα subunit has GTPase activity, which promotes the hydrolysis of GTP to GDP, and then repolymerizes with G$\beta\gamma$ dimer to form a heterotrimer at the original resting state (Dohlman and Thorner 2001). During this process, regulators of G-protein signaling (Rgs) proteins activate Gα to accelerate the hydrolysis of GTP by interacting with Gα subunits, resulting in the inactivation of G protein and subsequent shutdown of the G protein-mediated signaling pathway (Siderovski and Willard 2005; Zhang et al. 2011a). *M. oryzae* carries eight Rgs proteins (MoRgs1 to MoRgs8), where MoRgs5 to MoRgs8 were firstly identified in fungi. All Rgs proteins contain a conserved RGS domain, but the N-termini of MoRgs7 and MoRgs8 contain a seven transmembrane region like that in GPCR receptors (Zhang et al. 2011a) and the *Arabidopsis* AtRgs1 (Chen et al. 2003). Among the Rgs proteins, MoRgs1, MoRgs4, MoRgs6, and MoRgs7 regulate the recognition of physical cues and are important for conidial germination, germ tube growth, and appressorium formation. Deletion of *MoRGS* genes leads to abnormal appressorium formation at the tip of germ tubes (Liu et al. 2007; Zhang et al. 2011a). The transcription level of six *MoRGS* genes is regulated by the bZIP transcription factor (TF) MoBzip5, which is also involved in appressorium formation (Tang et al. 2015). Among these MoRgs proteins, MoRgs1 interacts with Gα subunit MagA to increase its GTPase activity and control intracellular cAMP levels to regulate host surface sensing. Deletion of *MoRGS1* leads to the formation of appressoria on hydrophilic (non-inducible) surfaces (Liu et al. 2007; Zhang et al. 2011a). During appressorium formation, intracellular MoRgs1 is phosphorylated by a casein kinase MoCk2, which enhances the GTPase-accelerating protein (GAP) activity of MoRgs1 to regulate intracellular cAMP levels and ultimately, controls appressorium formation. Meanwhile, the endoplasmic reticulum (ER) membrane protein complex, ER membrane complex (EMC) subunit MoEmc2, acts as a scaffold protein to build a platform for this process (Yu et al. 2021). MoRgs7 is phosphorylated by phosphokinase MoSep1 upon surface sensing (Feng et al. 2021; Xu et al. 2023), and then endocytosed into the cell. This step is mediated by an endocytosis-related protein MoCrn1 (coronin), which integrates the environmental cues into intracellular signals (Li et al. 2019b). The adenylate cyclase Mac1 and its associated protein Cap1 are subsequently activated. They catalyze cAMP synthesis to regulate appressorium formation (Zhou et al. 2012). Therefore, MoRgs proteins regulate intracellular cAMP levels by promoting the GTPase activity of Gα subunits to activate cAMP-dependent signaling pathway for host surface recognition and appressorium formation (Fig. 1).

The plasma membrane-localized receptor proteins Cbp1 and Msb2 interact with and activate the GTP-binding proteins Ras1 and Ras2. The activated Ras1 and Ras2 subsequently activate Pmk1 by interacting with Mst11 and Mst50, and regulate functional appressorium formation (Park et al. 2006; Liu et al. 2011; Zhou et al. 2014; Wang et al. 2015). Constitutive activation of Ras2 promotes its interaction with Mst11 and activates Mst11 through a phosphorylation cascade, resulting in aberrant activation of Pmk1-mediated MAPK and cAMP signaling pathways, thus inducing appressorium formation on hydrophilic surfaces (Zhou et al. 2014; Gong et al. 2015). In addition, the whisky protein MoWhi2 and phosphatase MoPsr1 co-localize at plasma membrane, where they negatively regulate the cAMP-PKA signaling pathway to control appressorium formation. Deleting either of them also leads to appressorium formation on hydrophilic surfaces (Shi et al. 2021).

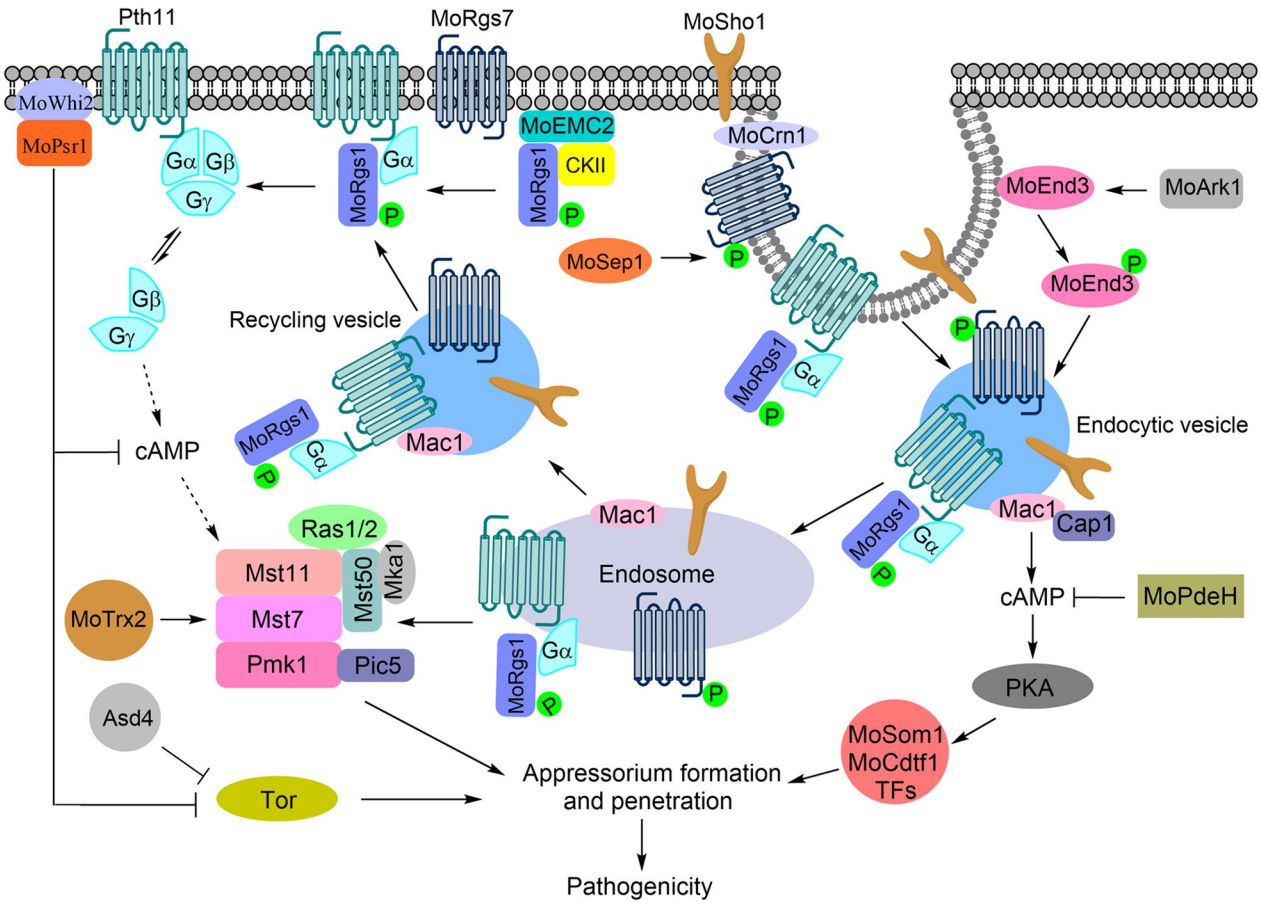

Fig. 1 The model of host surface signal recognition, integration, and intracellular transduction of *M. oryzae*. *M. oryzae* senses host physical cues, such as surface hardness and hydrophobicity by transmembrane receptor proteins, including Pth11, MoSho1, and MoRgs1. Upon sensing physical cues, receptor proteins are internalized by endocytosis-related proteins MoCrnl and MoEnd3 to activate the downstream cAMP-PKA signaling pathway and MAPK pathway, and ultimately, host physical cues are transduced to intracellular signals to activate the transcription of TFs that regulate functional appressorium formation

Internalization of host surface signals and intracellular signal transduction

Upon sensing host physical cues, Pth11, MoSho1, and MoWish that function upstream of either G-protein/cAMP signaling or the Pmk1-MAPK pathway, are translocated into cytosol through MoEnd3-mediated endocytosis (phosphorylated by actin-regulated kinase MoArk1) or coat protein complex II (COPII) cargo protein MoErv14 (Li et al. 2017b; Qian et al. 2023), while MoRgs7 is translocated into the cell through MoCrn1-mediated endocytosis (Li et al. 2019b). These proteins are endocytosed to form vesicles, and the vesicles are then translocated to early endosomes, late endosomes, and ultimately target membrane components to activate downstream signaling pathways (Ramanujam et al. 2013). This translocation process is regulated by MoVps39, a key member of the vacuole protein-sorting complex. Deletion of *MoVPS39* causes aberrant localization of receptor proteins, signal transduction, and appressorium formation (Ramanujam et al. 2013).

G protein/cAMP pathway and Pmk1-mediated MAPK pathway are two major signaling pathways for *M. oryzae* to transduce environmental cues into intracellular signals (Xu and Hamer 1996). The Pmk1-mediated signaling pathway consists of three protein kinases, Mst11 (MAPKKK), Mst7 (MAPKK), and Pmk1, and a scaffold protein Mst50 of Mst7 and Mst11. Each member plays a vital role in regulating appressorium formation, penetration, and infectious hyphal growth (Zhao et al. 2005; Park et al. 2006; Li et al. 2012; Zhou et al. 2014). Meanwhile, the MAPK activator MoMka1, an interacting protein of Mst50, controls appressorium formation by modulating the phosphorylation of Pmk1 (Lv et al. 2022). In addition, thioredoxin Trx2 regulates the phosphorylation of Pmk1 by interacting with Mst7, which affects appressorium formation (Zhang et al. 2016b). Pic5 interacts with Pmk1 and functions in the terminal commitment of deformed

germ tubes to form appressoria that are arrested in the G1 stage. Deletion of *PIC5* results in the formation of chains of appressoria or appressorium-like structures (Zhang et al. 2011b).

Appressorium formation and fungal pathogenicity are highly associated with the cAMP-PKA signaling pathway in *M. oryzae*. Upon sensing physical cues, plasma membrane-localized receptors activate the G*α* subunit rapidly and subsequently activate adenylate cyclase Mac1 for the synthesis of cAMP from ATP, where cAMP acts as a second messenger to activate the cAMP-PKA signaling pathway (Mitchell and Dean 1995; Choi and Dean 1997; Dean et al. 2005). PKA proteins form heterotetramer with two regulatory subunits and two catalytic subunits (Selvaraj et al. 2017). It is disassembled after sensing cAMP, leading to the activation of the downstream TFs, MoSom1 and MoCdtf1, to regulate appressorium formation (Yan et al. 2011). Knocking out the adenylate cyclase encoding gene *MAC1* results in a significant decrease of intracellular cAMP levels, and as a result, *M. oryzae* fails to recognize physical cues to form appressorium (Choi and Dean 1997). This phenotype is also observed in the absence of Ric8, a regulatory factor interacting with G*α* subunit MagB. Of note, exogenous cAMP treatment is able to partially or completely restore the appressorium formation of *Δmac1*, *ΔmagB*, and *Δric8* mutants (Li et al. 2010). During this event, phosphodiesterase MoPdeH is critical in balancing intracellular cAMP levels. Deletion of *MoPDEH* leads to an increased intracellular cAMP level and appressorium formation on the hydrophilic surfaces (Ramanujam and Naqvi 2010; Zhang et al. 2011c; Yang et al. 2018b).

In addition to cAMP/PKA and Pmk1 pathways, the target of rapamycin (TOR) signaling pathway is also involved in appressorium formation. For example, the activation of the TOR signaling pathway by intracellular glutamine blocks functional appressorium formation (Marroquin-Guzman and Wilson 2015). Deletion of GATA TF encoding gene *ASD4* activates the TOR signaling pathway and results in abnormal appressorium formation. Exogenous rapamycin can compensate the defect of appressorium formation in both *Δasd4* and *Δcpka* mutants but not in the *Δpmk1* mutant (Marroquin-Guzman and Wilson 2015). Besides, deleting *MoWHI2* or *MoPSR1* also activates the TOR pathway and leads to abnormal appressorium formation, which can also be suppressed by exogenous rapamycin (Shi et al. 2021).

Cell wall integrity (CWI) and high osmotic glycerol (HOG) signaling pathways are two conserved MAPK pathways (Li et al. 2012). An unknown plasma membrane-localized receptor, which functions upstream of the CWI pathway, senses cell-wall stresses to activate the Mck1-Mkk1-Mps1 protein kinase cascade through GEF Rom2, GTPase Rho1, and protein kinase C Pkc1. The Mck1-Mkk1-Mps1 protein kinase cascade activation results in the transduction of extracellular stress signals into the cell and the activation of downstream TFs (Jendretzki et al. 2011). Deleting any component of the Mck1-Mkk1-Mps1 cascade leads to an increased sensitivity to cell-wall stresses and the loss of capacity to penetrate the host epidermis by appressoria (Xu et al. 1998; Jeon et al. 2008; Yin et al. 2016). Mkk1 also mediates the crosstalk of the CWI pathway, HOG pathway, unfolded protein response (UPR), and autophagy (Yin et al. 2016; Yin et al. 2019a, b). Mps1 activates the transcription of downstream pathogenicity-related TFs Mig1 and MoSwi6 (Mehrabi et al. 2008; Qi et al. 2012). Osm1, a key protein kinase of the HOG pathway, plays a crucial role in response to hyperosmotic stress but not in appressorium formation and fungal pathogenicity (Dixon et al. 1999). However, the proteins at the upstream of this pathway, such as Sln1, are involved in stress responses and pathogenicity, suggesting the presence of additional downstream target proteins except Osm1 in *M. oryzae* (Motoyama et al. 2008; Zhang et al. 2010).

Histone acetyltransferases are characterized to regulate the differentiation of functional appressorium in *M. oryzae*. During vegetative growth, histone acetyltransferase MoHat1 is phosphorylated by glucokinase MoGsk1 and is accumulated in the nucleus (Yin et al. 2019a). Upon infection, a portion of MoHat1 in *M. oryzae* is rapidly dephosphorylated and translocated into cytoplasm under the assistance of chaperone MoSsb1. The cytoplasmic MoHat1 acetylates two key autophagy proteins MoAtg3 and MoAtg9 to regulate autophagy and affects the translocation and degradation of glycogens and lipids, as well as functional appressorium formation and pathogenicity (Yin et al. 2019a).

In addition, sphingolipid biosynthesis pathway is reported to play a crucial role in appressorium differentiation. Ceramide compounds of this pathway are essential for normal mitosis-controlled appressorial development. Deletion of *MoLAG1*, the encoding gene for de novo synthesis of ceramide, showed impaired mycelial growth, decreased conidiation, and abnormal appressorium; as a result, the mutant is unable to penetrate host surface. Supplementing exogenous ceramide can restore the pathogenicity defect of the *ΔMolag1* mutant (Liu et al. 2019a). VASt domain-containing protein MoVast2 plays a role in appressorium development and virulence by interacting with MoVast1 and MoAtg8, which collectively maintains lipid homeostasis and autophagy balance by regulating TOR activity in *M. oryzae* (Zhu et al. 2023). In addition, AGC kinase MoFpk1 regulates appressorium development likely by responding to membrane stress and

autophagy through lipid asymmetry maintenance (Wu et al. 2022).

Cell cycle and autophagy regulate appressorium formation

In addition to cAMP and MAPK pathways, *M. oryzae* has also evolved other intracellular signaling pathways to regulate functional appressorium formation. For instance, cell cycle and autophagy are involved in conidium germination and appressorium formation (Veneault-Fourrey et al. 2006; Saunders et al. 2010). The fungal conidia usually consist of three cells, each of which has one nucleus. During appressorium formation, the nucleus in the apical cell undergoes a single mitotic event to produce two daughter nuclei. One migrates into the nascent appressorium, and a septum is immediately formed, and the other one migrates back to the conidium (Saunders et al. 2010). The initiation of appressorium from the tip of the germ tube is controlled by DNA replication in the S phase of mitosis. Exogenous hydroxyurea (HU) or knocking out temperature-sensitive gene *NIM1* to block DNA replication prevents the germ tubes from differentiating into appressoria (Saunders et al. 2010). *M. oryzae* has evolved two independent S-phase regulatory systems to ensure the maturation of appressoria. The first one is the DNA damage-response (DDR) pathway mediated by protein kinase Cds1. The second one is independent of the DDR pathway, and regulates the formation of penetration peg and the extension of invasive hyphae, which is mainly through sensing turgor pressure and melanin biosynthesis (Oses-Ruiz et al. 2017). Following the S phase, G2/M cell cycle checkpoints are critical for appressorium maturation and plant infection (Saunders et al. 2010). Inactivating TOR pathway arrests the cell cycle in G2 phase, which is required for autophagy and appressorium formation. Nutrients recycled from autophagy reactivate the TOR pathway to reinitiate cell cycle progression. Due to the re-inactivation of the TOR pathway, the nucleus in the appressorium is arrested in the G1 phase (Marroquin-Guzman et al. 2017). After appressorium formation, nuclei in conidia are degraded through autophagy, and the resulting degradation products are recycled into appressorium (Kaschani et al. 2010; He et al. 2012). In addition, Tpc1, a TF that controls polar growth and virulence of *M. oryzae*, is found to be involved in multiple biochemical processes, including autophagy, glycogen/lipid degradation, and septin-mediated remodeling of F-actin cytoskeleton. Tpc1 regulates the transcription of genes in Pmk1 and autophagy signaling pathways, thereby controlling functional appressorium formation and pathogenicity (Galhano et al. 2017; Jenkinson et al. 2017; Pfeifer and Khang 2018).

Cytoskeleton remodeling regulates appressorium formation and penetration

During appressorium maturation, reactive oxygen species (ROS) is generated to strengthen the cell wall (Egan et al. 2007). The generation of intracellular ROS is directly regulated by two NADPH oxidases, Nox1 and Nox2. Deleting either of them results in defects in appressorial penetration (Dagdas et al. 2012). Once appressorium is matured, the intracellular actin cytoskeleton is remodeled to form a toroidal F-actin network at the base of the appressorium, which is scaffolded by septin GTPases. The F-actin network regulates the extension of the plasma membrane and transforms the homogeneous turgor pressure within the appressorium into a directional physical force, which promotes the formation of penetration peg and subsequent penetration into rice epidermis (Dagdas et al. 2012). When the intracellular turgor pressure reaches a threshold, the plasma-membrane kinase Sln1 serves as a turgor pressure sensor to inhibit the biosynthesis of melanin and glycerol in appressorium and to halt the increase of the intracellular turgor pressure. Through the Pkc1-dependent cell integrity pathway, Sln1 activates NADPH oxidase and recruits septin to the appressorium pore to accelerate the remodeling of the F-actin network at the base of the appressorium (Ryder et al. 2019). Meanwhile, Sln1 controls appressorium membrane tension to maintain normal turgor pressure. Deletion of *SLN1* results in an abnormal membrane tension during inflation of the appressorium and an abnormal increase of intracellular turgor pressure, which leads to significant decrease for the appressorium to penetrate host epidermis (Zhang et al. 2010; Ryder et al. 2019, 2023).

The accurate assembly of the F-actin network is required to maintain appressorium turgor pressure and penetration. Remodeling of the F-actin network involves multiple intracellular components. F-actin capping protein MoCapA/B heterodimer and endocytic protein MoEnd3 are directly involved in the dynamic assembly of F-actin/Septin network at the base of the appressorium. Deletion of either subunit of the *MoCAPA/B* heterodimer or *MoEND3* causes abnormal assembly of F-actin, as well as decreased appressorium turgor pressure and reduced penetration. Actin-regulating kinase MoArk1 regulates its binding to F-actin by phosphorylating MoCapA/B dimer and endocytic protein MoEnd3, thereby controlling the assembly of F-actin network (Li et al. 2017a, 2017b). MoAbp1, a scaffold protein that interacts with F-actin, recruits protein kinase MoArk1 and adenylate cyclase-associated protein MoCap1 to the cytoskeleton assembly platform, and regulates the assembly of F-actin network during appressorium differentiation (Zhou et al. 2012; Li et al. 2019b).

Molecular mechanisms of *M. oryzae* infection through subverting basal immunity in rice

During appressorium maturation, turgor pressure is generated in the appressorium to promote the formation of penetration peg, which penetrates the host epidermis (Wilson and Talbot 2009). Then, a thin primary invasive hypha is differentiated and expanded within the living rice cells. During the early infection stage, the primary invasive hypha uptakes nutrients from the living rice cells and further differentiates into bulbous invasive hyphae. The invasive hyphae are surrounded by rice plasma membrane, in which it forms an enclosed apoplastic space called extra-invasive hyphal membrane (EIHM) (Khang et al. 2010). The bulbous invasive hyphae rapidly expand in the first infected cell and then spread into neighboring cells, potentially through the host plasmodesmata (Sakulkoo et al. 2018).

During the co-evolution with *M. oryzae*, rice has evolved multilayered immune system to defend against the fungal pathogen. The immune activation includes pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI). PTI involves several basal responses triggered by the recognition of PAMPs, which is mediated by plasma membrane-localized pattern-recognition receptors (PRRs) (Monaghan and Zipfel 2012). Pathogens secrete effectors to interfere with PTI responses and induce effector-triggered susceptibility (ETS) in plants. Plants subsequently have evolved the cognate resistance proteins, which directly or indirectly sense effectors to initiate more robust and effective defense responses, the ETI (Jones and Dangl 2006).

PAMP-triggered immunity

PTI is usually accompanied by ROS burst, callose accumulation, activation of MAPK signaling pathway, and transcriptional reprogramming of defense genes (Nurnberger and Kemmerling 2009). It is a durable and broad-spectrum disease resistance system (Xiao and Wang 1997; Li et al. 2004; Dodds and Rathjen 2010). During plant-fungal interactions, the fungal cell wall, on one hand, acts as a natural barrier to protect itself from environmental stress (Li et al. 2004). On the other hand, chitin and β-glucan in fungal cell walls can also be recognized as PAMPs by host PRRs to trigger PTI (Latgé 2007; Gow et al. 2017).

As a classical PAMP, the chitin oligosaccharides-triggered PTI signaling pathway has been well studied. OsCEBiP, the receptor of chitin oligosaccharides in rice, has been identified. Silencing of *OsCEBiP* attenuates chitin oligosaccharide-induced immune responses (Ito et al. 1997; Kaku et al. 2006). Two extracellular LysM motifs of OsCEBiP are responsible for its binding to chitin. In addition, two OsCEBiP proteins and two transmembrane protein kinase OsCERK1s form a heterotetramer. Upon chitin oligosaccharides recognition, the heterotetramer regulates the phosphorylation of a downstream protein kinase OsRLCK185, which ultimately triggers immune responses (Hayafune et al. 2014; Wang et al. 2017).

To successfully invade plant cells, pathogens have evolved a complicated system to overcome chitin oligosaccharide-induced PTI, including the secretion of various effectors to interfere with plant immune responses (Hayafune et al. 2014). For instance, *M. oryzae* secretes *N*-glycosylated Slp1, an effector with LysM domain, to interfere with chitin oligosaccharide-induced PTI (Mentlak et al. 2012; Chen et al. 2014). Therefore, it is important to identify effectors and their host targets, and investigate the molecular mechanisms of plant-pathogen interaction. This knowledge will not only advance our understanding of pathogenesis of the pathogen, but also provide new avenues for breeding disease-resistance rice cultivars.

Structures of *M. oryzae* effectors

With the development of molecular biology and bioinformatics, more and more effectors have been identified in *M. oryzae*. Bioinformatics analyses show that *M. oryzae* secretes over 1500 proteins, including cell wall-degrading enzymes, such as chitinase and glucanase, and extracellular enzymes involved in protein modification and redox balance (Yoshida et al. 2009; Dong et al. 2015). These effectors and extracellular enzymes interfere with host immunity and promote fungal infection by targeting host resistance- or susceptibility-associated proteins in cytoplasm, organelles or apoplastic spaces (Dong et al. 2015).

No evidently conserved domains or motifs have been identified among most *M. oryzae* effectors. However, recent studies revealed that some effectors secreted by *M. oryzae* and other fungi, including avirulence proteins AvrCO39 and AvrPia, have a conserved *Magnaporthe* Avrs and ToxB-like (MAX) structure. So far, half of the cloned avirulence effectors in *M. oryzae* contain the MAX structure (de Guillen et al. 2015; Maqbool et al. 2015; Zhang et al. 2018), demonstrating the evolutional diversity of fungal effectors.

Biosynthesis, translocation, and secretion of *M. oryzae* effectors

M. oryzae secretes a large repertoire of effectors into rice cells to suppress host immune responses and promote its infection (Kamoun 2007; Laflamme 2023; Yan et al. 2023). However, mechanisms of the biosynthesis, translocation, and secretion of the effectors remain unclear. Previous studies showed that pathogens are able to sense

extracellular host signals at the early infection stage and transduce these signals to the nucleus through endocytosis and vesicle translocation, which ultimately activates TFs to regulate the transcription of effectors. Synthesized effectors are secreted into host cells through vesicle translocation to inhibit host immunity and promote fungal infection (Bielska et al. 2014). At the early infection stage, unknown plasma membrane-localized receptors of *M. oryzae* sense rice-produced ROS, which leads to the phosphorylation of intracellular protein kinase MoOsm1. The phosphorylated MoOsm1 enters nucleus to phosphorylate TF MoAtf1 (Guo et al. 2010), and dissociates MoAtf1 from transcriptional repressor MoTup1, as a result activating the expressions of antioxidant genes in response to host-derived ROS (Liu et al. 2019b). Simultaneously, cytosolic protein phosphatase MoYvh1 enters the nucleus with the assistance of chaperone proteins MoSsb1 and MoSsz1 (Yang et al. 2018a), and competes with ribosomal protein MoMrt4 for the binding on ribosome precursor, which facilitates ribosome maturation and promotes the biosynthesis of a large repertoire of secreted proteins in response to external ROS stress (Liu et al. 2018). In addition, Rgs1 is proved to be a novel transcriptional regulator to regulate a large group of effector genes, and the regulation is independent of its G-protein signaling during infection (Tang et al. 2023).

Based on their localization in plant cells, effectors can be characterized into two groups, the cytoplasmic effectors and the apoplastic effectors (Giraldo et al. 2013). Specific domains or motifs related to the subcellular localization have not yet been found in effectors, making it difficult to distinguish these two types based on their amino acid sequences. During *M. oryzae* infection, cytoplasmic effectors, such as Avr-Pita, Avr-Pia, Pwl1, Pwl2, Bas2, AvrPiz-t, and Avr-Pi9, are accumulated in biotrophic interfacial complex (BIC) and then are secreted into host cells. The BIC structure, a pathogen-induced and host-derived membrane-rich structure, mainly develops at the tip of primary invasive hyphae of *M. oryzae* (Khang et al. 2010). After primary invasive hyphae are differentiated into secondary invasive hyphae, the BIC structures localize at a subapical position of the newly developed invasive hyphae. Effectors within BICs are packaged into punctate membranous effector compartments and are translocated into host cytoplasm by plant clathrin-mediated endocytosis. The effectors then enter adjacent cells to interfere with host immunity, ultimately facilitating the extension of invasive hyphae in adjacent host cells (Khang et al. 2010; Oliveira-Garcia et al. 2023).

The secretion of apoplastic effectors, including Bas4, Avr1-CO39, and Slp1, is not dependent on BIC but mainly relies on the canonical ER-Golgi pathway, which secretes apoplastic effectors into EIHM space (Khang et al. 2010; Giraldo et al. 2013). Cytoplasmic effectors are translocated into BIC via the exocytosis complex and membrane fusion-associated t-SNARE proteins, which then are released into host cells. This pathway is distinct from the Golgi-regulated exocytosis pathway. Deletion of exocytosis complex components *SEC5* and *EXO70* affects the proper translocation of cytoplasmic effectors to BIC, and thus reduces fungal pathogenicity. However, mutation of *SEC5* and *EXO70* have no effect on the secretion of apoplastic effectors. However, mutation of t-SNARE protein encoding gene *SSO1* results in abnormal formation of BIC and subsequently reduces fungal pathogenicity (Giraldo et al. 2013).

M. oryzae proteins can be secreted out through multiple pathways (Spang 2004; Abubakar et al. 2023). Previous studies found that the ER chaperone protein Lhs1 regulates the secretion of cytoplasmic effector Avr-Pita (Yi et al. 2009). SNARE proteins MoSec22 and MoVam7 regulate vesicular trafficking and balance endocytosis and secretion. For instance, they affect the secretion of extracellular laccases and peroxidases (Song et al. 2010; Dou et al. 2012). Additionally, they regulate the secretion of avirulence effectors Avr-Pia and AvrPiz-t by influencing the localization of MoEnd3, an endocytosis-related protein (Li et al. 2017b). Likewise, the Qc-SNARE protein MoSyn8 regulates the secretion of Avr-Pia and AvrPiz-t, in which they failed to accumulate in the BIC and cannot be secreted into host cells when *MoSYN8* is knocked out (Qi et al. 2016). Recent studies revealed that *M. oryzae* effectors are sorted by ER-derived COPII vesicles after being synthesized by ribosomes, and this process is dependent on MoErv29, a receptor of COPII vesicles. MoErv29 specifically recognizes the tripeptide motif adjacent of the signal peptide in effectors, which could sort different effectors into different vesicles for translocation (Qian et al. 2022). In addition, vesicle depolymerization factor MoSwa2 interacts with COPII vesicle component MoSec24-2 to promote the depolymerization of COPII vesicles, and thus regulating the secretion of cytoplasmic and apoplastic effectors (Liu et al. 2021a). Recently, we found that the ergosterol biosynthesis protein MoErg4 is involved in regulating plasma membrane integrity in *M. oryzae*. Defect in ergosterol biosynthesis disrupts lipid raft formation in the plasma membrane and causes maldistribution of SNARE protein MoSso1. The latter inhibits its interaction with the v-SNARE protein MoSnc1. Besides, we found that MoSso1-MoSnc1 interaction is important for BIC development and cytoplasmic effector secretion (Guo et al. 2022). Coincidentally, Chen et al. dissect the role of MoRab7/Retromer/MoSnc1 sorting machinery in effector secretion and virulence in *M. oryzae*, where they discover that MoRab7 recruits the retromer complex to the vacuolar

membrane, enabling recognition of a family of SNARE proteins, and recruits MoSnc1 to establish a membrane conduit/interface which is essential for effector secretion (Chen et al. 2023). In addition, a recent study reveals an unconventional secretion route of effectors which is regulated by tRNA modification and codon usage control. Uba4-Urm1 sulfur relay system mediates tRNA anticodon wobble uridine 2-thiolation (s^2U_{34}), a conserved modification required for efficient decoding of AA-ending cognate codons. Loss of s^2U_{34} abolished the translation of AA-ending codon-rich messenger RNAs, which encode unconventionally secreted cytoplasmic effectors (Li et al. 2023a). The main progresses of biosynthesis, translocation, and secretion of effectors in *M. oryzae* are shown in Fig. 2. *M. oryzae* effectors have been known to be secreted out of the cells through two distinct secretory

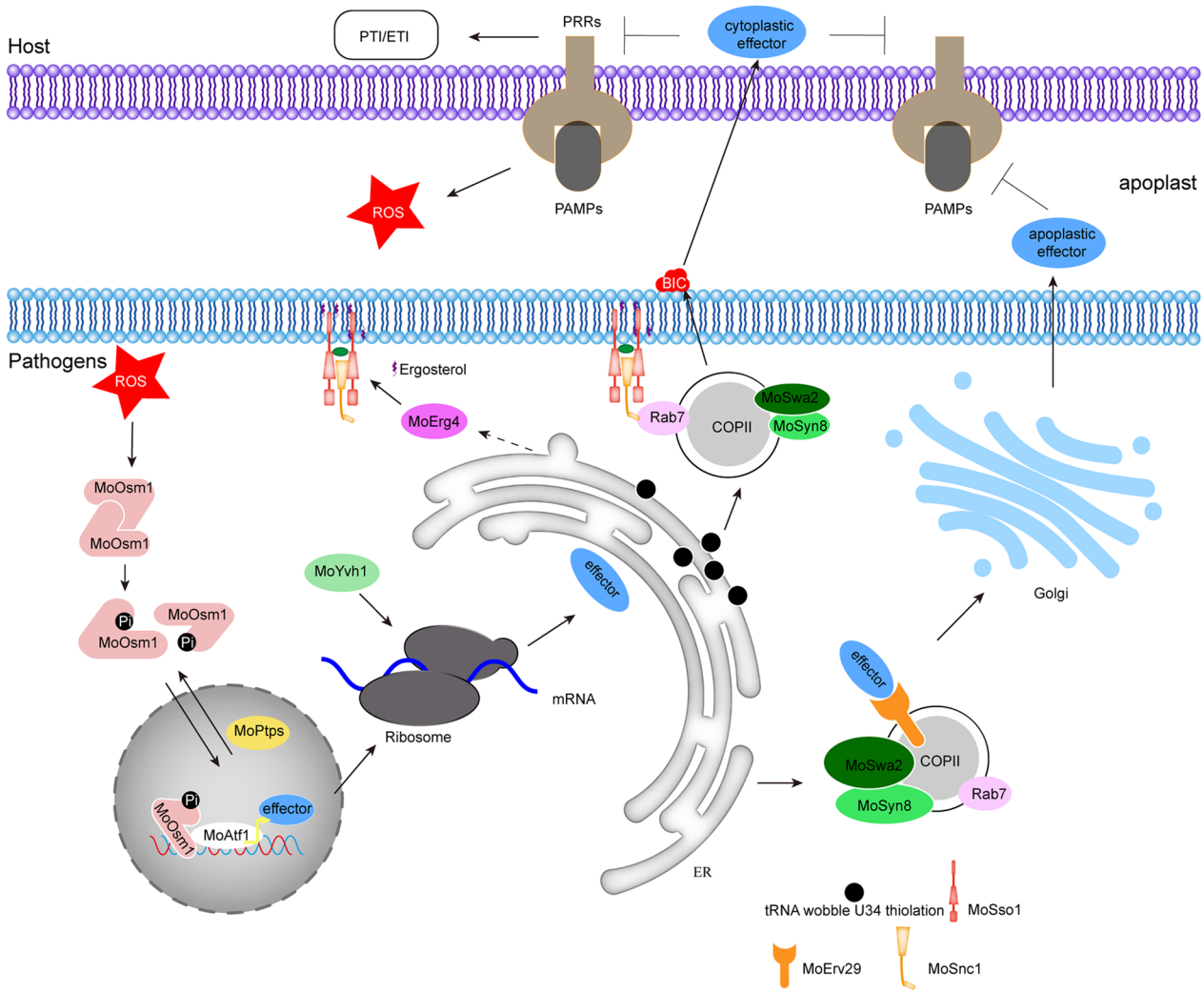

Fig. 2 The model of biosynthesis, translocation, and secretion of effectors in *M. oryzae*. During the early stage of *M. oryzae*-rice interaction, the protein kinase MoOsm1 is phosphorylated and enters the nucleus as monomers upon recognizing host ROS. Then, MoOsm1 phosphorylates the TF MoAtf1 and dissociates MoAtf1 from a transcriptional repressor MoTup1, leading to the transcription of antioxidant genes in response to host ROS accumulation. MoAtf1 simultaneously activates the expression of phosphatase MoPtp1/2, which in turn dephosphorylates MoOsm1. After dephosphorylation, MoPtp1/2 exits from the nucleus and forms dimers in the cytosol. Meanwhile, the cytoplastic MoYvh1 accelerates the maturation of ribosomes to facilitate the biosynthesis of effectors in response to external ROS. The synthesized effectors are further processed in ER, where the signal peptide of effectors is cleaved and the N-terminal tri-peptide motif is thus exposed to ER membrane complex protein MoErv29 for further sorting into distinct vesicles. When effectors are encapsulated in vesicles, de-polymerization factor MoSwa2 interacts with COPII vesicle component protein MoSec24-2 to regulate the depolymerization of COPII vesicles and promote the fusion of COPII with the target membrane. MoErg4 regulates ergosterol biosynthesis and plasma membrane integrity, which are important for lipid raft formation and the interaction of MoSso1 and MoSnc1. They collectively modulate BIC development and cytoplasmic effector protein secretion. As a result, the effectors are secreted into apoplastic space or host cytoplasm, which subsequently suppresses host immune responses

pathways. Further investigation on how effectors are secreted and how they function in plants will deepen our understanding of the pathogenesis of *M. oryzae*.

Mechanisms of *M. oryzae* effectors in suppressing host immune responses

During the arms race with rice, *M. oryzae* secretes a large repertoire of effectors into rice cells to subvert host immunity. For example, both apoplastic effectors Slp1 and MoAa91 compete with plasma membrane localized receptor OsCEBiP for binding to chitin oligosaccharides, thereby evading host recognition and subsequent chitin-induced immune responses (Mentlak et al. 2012; Li et al. 2020a). Strain-specific effectors MoIug6 and MoIug9 are secreted into host cells through BIC structures to repress the expression of salicylic acid-induced defense responsive genes (Dong et al. 2015). Avirulence effector AvrPiz-t inhibits flg22- or chitin-induced ROS burst and other defense responses (Qian et al. 2022). AvrPiz-t has been found to target multiple proteins in rice to inhibit host immune response (Park et al. 2012, 2016; Zhang et al. 2022a). It interacts with two RING E3 ligases APIP6 and APIP10 in rice, suppressing their activity to promote protein degradation. For example, APIP10 promotes the degradation of a rice NB-LRR protein Piz-t. Knocking out or silencing *APIP10* causes the excessive accumulation of Piz-t and the associated cell death (Park et al. 2016). AvrPiz-t also interacts with bZIP TF APIP5 and represses its transcriptional activity. It is massively accumulated during the necrotrophic stage of infection (Wang et al. 2016). APIP5 functions as a TF and an RNA-binding protein to modulate cell death and immunity in rice. It targets two genes that positively regulate blast resistance: the cell wall-associated kinase gene *OsWAK5* and the cytochrome P450 gene *CYP72A1*. Meanwhile, APIP5 acts as an RNA-binding protein to regulate mRNA turnover of the cell death- and defense-related genes *OsLSD1* and *OsRAC1* (Zhang et al. 2022a). Silencing of *APIP5* causes cell death. Simultaneously, expression of AvrPiz-t facilitates cell death in rice. By contrast, Piz-t and APIP5 stabilize each other and prevent cell death during necrotrophic stage (Wang et al. 2016; Zhang et al. 2022a). This finding reveals that plant NLR protein can inhibit effector-triggered necrosis during the necrotrophic stage. AvrPiz-t also interacts with rice nucleoporin APIP12 to inhibit its function and the expression of defense-related genes, thereby reducing the resistance to *M. oryzae* (Tang et al. 2017). Furthermore, AvrPiz-t can mimic the structure of a rice disease resistance-related protein ROD1 to scavenge host ROS, and thus suppress host immunity (Gao et al. 2021). These findings demonstrate that AvrPiz-t is multifunctional. It has multiple target proteins in rice. In addition, AvrPi9 degrades rice deubiquitinase PIC1 to repress PIC1-mediated immune responses. It affects the stability of OsRGLG5, a RING-type E3 ubiquitin ligase, which positively regulates basal resistance to rice blast disease (Zhai et al. 2022; Liu et al. 2023). Likewise, AvrPii targets multiple host proteins, including two EXO70 proteins and a NADP malic enzyme 2 (Os-NADP-ME2), to inhibit rice immune responses through different pathways (Fujisaki et al. 2015; Singh et al. 2016; De la Concepcion et al. 2022). In addition, the secreted chitinases MoChi1 and MoChia1 contain effector-like functions and can also compete with receptors OsMBL1 and OsCEBiP for sensing chitin, thus interfering with host immune responses (Han et al. 2019; Yang et al. 2019).

M. oryzae effectors can target different subcellular organelles to interfere with host immune responses. For example, MoHTR1 and MoHTR2 are translocated into the host nucleus and control the transcription of rice defense-related genes, which suppresses host immunity and promotes infection (Kim et al. 2020). AvrPiz-t can target rice transmembrane K^+ channel and inhibit the function of OsKAT in K^+ transportation, thereby repressing rice resistance to *M. oryzae* (Shi et al. 2018). Besides, AvrPiz-t interacts with Bowman-Birk protease inhibitor APIP4 in 26S proteasome and inhibits its E3 ligase activity (Zhang et al. 2020). Another effector MoCDIP4 interferes with the complex assembly of a dynamin-related protein OsDRP1E and a mitochondria-related protein OsDjA9 by interacting with OsDRP1E, leading to the abnormal mitochondrial development and decreased disease resistance (Xu et al. 2020). The main discoveries for *M. oryzae* effectors in suppressing host immune responses are shown in Fig. 3.

To counteract the inhibition of PTI by effectors, plants have evolved a more efficient and specific immune system-mediated response called ETI to directly or indirectly recognize fungal effectors and trigger a more robust immune response, usually accompanied by programmed cell death (Chisholm et al. 2006; Jones and Dangl 2006; Liu et al. 2013). ETI is mainly initiated by NLR proteins, which constitute the largest family in plants, with about 400 members in rice. So far, more than 20 blast disease resistance NLR genes in rice and 12 Avr genes from *M. oryzae* have been identified (Fernandez and Orth 2018). NLR proteins directly or indirectly interact with Avr effectors to trigger host immune responses, and the direct interactions include Pita/AvrPita, Pik/AvrPik, Pia/AvrPia, and PiCO39/AvrCO39 pairs. For instance, Pita is a cytoplasmic NLR receptor. The cognate AvrPita protein in *M. oryzae* is a zinc-dependent metalloprotease (Orbach et al. 2000). Pita recognizes AvrPita via its C-terminal LRR to trigger immune response in rice (Jia et al. 2000). However, some NLR proteins cannot

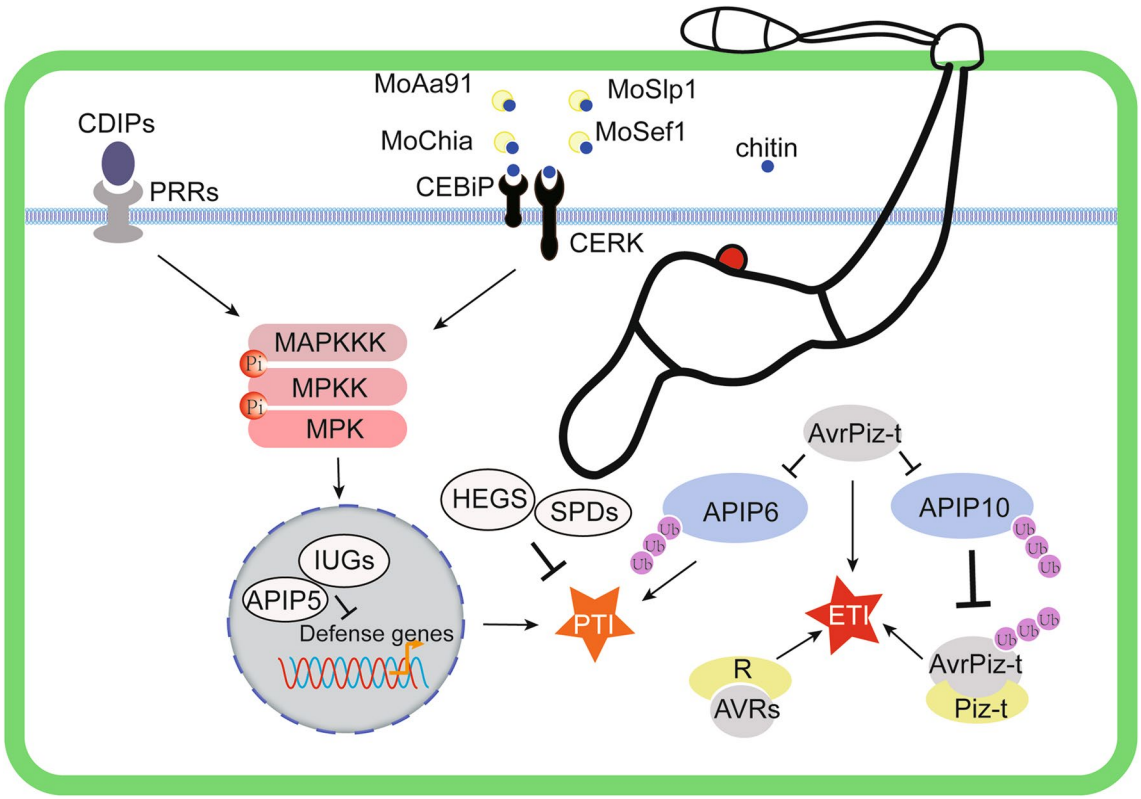

Fig. 3 The model of *M. oryzae* effectors in suppressing host immune responses. Rice pattern recognition receptors OsCEBiP and OsCERK1 recognize *M. oryzae* cell wall-derived chitin oligosaccharides to activate PTI through the MAPK cascade pathway. To successfully invade rice, *M. oryzae* has evolved well-established systems to overcome chitin oligosaccharides-triggered PTI. For example, apoplastic effectors Slp1 and MoAa91, as well as chitinase MoChia1, compete with OsCEBiP for binding to chitin oligosaccharides, masking the recognition of chitin oligosaccharides by OsCEBiP, thereby evading host immune responses. Meanwhile, many avirulence proteins secreted by *M. oryzae* interfere with PTI by inhibiting the function of host proteins. During the long-term arms race with *M. oryzae*, rice has evolved specific Resistance (*R*) proteins or nucleotide-binding leucine-rich repeat (NLR) receptors to recognize fungal Avr proteins, initiating ETI and boosting host resistance

directly interact with Avr effectors and their recognition is dependent on other host proteins, such as Pii/AvrPii and Piz-t/AvrPiz-t pairs (Park et al. 2012). AvrPii specifically interacts with rice exocytosis complex-related protein OsEXO70 and a malic enzyme OsNADP-ME2-3. Silencing either *OsEXO70* or *OsNADP-ME2-3* in the Pii-containing rice line results in the inability of Pii to recognize AvrPii, which subsequently abolishes the disease resistance against pathogens harboring AvrPii (Zhang et al. 2020). Therefore, identifying NLR and avirulence genes, and dissecting the mechanism of their interaction are critical for developing new disease control strategies. For example, engineering the heavy metal associated (HMA) domain of NLR proteins expands the recognition of multiple effectors (De la Concepcion et al. 2018; De la Concepcion et al. 2019; Liu et al. 2021c).

In addition, *M. oryzae* is composed of host-specific subgroups, such as the *Oryza*, *Eleusine*, *Avena*, and *Lolium* pathotypes that cause disease in rice, finger millet, oat, and perennial ryegrass, respectively (Kato, et al. 2000; Oh et al. 2002; Tosa et al. 2004). For example, host-specific effectors AVR-Pwt3 and AVR-Pwt4, whose gene products elicit defense in wheat cultivars containing the corresponding resistance proteins Rwt3 and Rwt4. Studies on avirulence and resistance protein distributions suggest that wheat blast emerged due to widespread deployment of *rwt3* wheat, followed by the loss of AVR-Pwt3. This study implies that host-specific effectors serve as a springboard for the host jump between plants (Tosa et al. 2017).

Potential control strategies of rice blast based on *M. oryzae*-rice interaction mechanism

Research on durable management of rice blast disease is challenging. Currently, deployment of high-yield rice cultivars carrying single dominant disease resistance (*R*) gene in the field servers as the most effective means of controlling rice blast disease, which satisfies the "gene-for-gene" model (Skamnioti and Gurr 2009). However, *M. oryzae* races can evolve rapidly under selection

pressure to escape from host recognition. Consequently, single-locus resistance is often short-lived and lasts for only 2–4 years in field, especially in large acreages of genetically uniform rice cultivars (Bonman et al. 1992). To resolve this challenge, an effective solution is to track the variation of *AVR* genes in the filed pathogen population, which can provide vital information for how to release and rotate blast-resistant rice cultivars (Fernandez and Orth 2018). Meanwhile, planting diversified cultivars with different *R* genes or the multiline varieties consisting of blast resistant isogenic loci in the same area can also maintain resistance to blast disease in rice (Zhang et al. 2022a, b, c). Furthermore, an alternative way to control rice blast disease is to deploy broad-spectrum blast resistance genes or using genome editing technique to create disease resistance rice cultivars, which has been proved to be effective and innovative (Were and Talbot 2023).

During the last decade, a few broad-spectrum blast resistant genes were identified in rice (Liu et al. 2021b). The key examples are as follows: (1) the natural allele of a C_2H_2-type transcription factor *bsr-d1* was identified and conferred with non-race-specific resistance to blast disease (Li et al. 2017a, b; Zhu et al. 2020); (2) the MYB transcription factor OsMYB30 is involved in *bsr-d1*-mediated broad-spectrum blast resistance by activating the lignin biosynthesis genes *Os4CL3* and *Os4CL5* to strengthen cell walls (Li et al. 2020b); (3) the RING protein OsBBI1 confers broad-spectrum resistance against *M. oryzae* by increasing ROS accumulation in cells and reinforcing the cell-wall defense during infection (Li et al. 2011); (4) the light-harvesting complex II protein LHCB5 is involved in light regulation of resistance to *M. oryzae* and its phosphorylation enhances broad-spectrum resistance of rice to *M. oryzae* through the accumulation of ROS in chloroplast (Liu et al. 2019c); (5) the ubiquitin-conjugating enzyme OsUBC45 promotes broad-spectrum disease resistance and yield in rice by enhancing the degradation of glycogen synthase kinase OsGSK3 and aquaporin OsPIP2;1, the negative regulators of grain size and basal immunity, respectively (Wang et al. 2023).

Genome editing is a transformational technology that alters the coding or regulatory sequence of a specific gene accurately, enabling us to change specific traits of organisms (Were and Talbot 2023). It has demonstrated the great potential for genome editing in identifying and deploying novel disease resistance sources. For example, genome editing technique has been used to characterize a gene associated with a novel mechanism of disease resistance (Sha et al. 2023). They found that a lesion mimic mutant was associated with a single gene named RESISTANCE TO BLAST1 (RBL1). The *rbl1* mutant was resistant to rice blast disease but with significant reduction in yield. Genome editing by producing a variant of RBL1 (RBL1Δ12) not only restores the growth and yield of edited rice lines, but also bestows multi-disease resistance, including blast disease (Sha et al. 2023). This finding is a breakthrough, and suggests that we can enhance disease resistance by editing rice genome.

Fungicide application is another effective strategy to control rice blast disease. The fungicide structures and the method of application define their efficacy. The most commonly used fungicides to control blast disease in global markets are Probenazole, Meiji Seika, Tricyclazole, DowAgrosciences, Azoxystrobin, Isoprothiolane, Nihon Nohyaku, and Propiconazole (Skamnioti and Gurr 2009). Nevertheless, the blast pathogens develop tolerance against chemical fungicides rather rapidly, which are largely due to the rapid mutations among *M. oryzae* races. Notably, the extensive use of a single pesticide in the field significantly facilitates the mutation. Recently, accumulating studies focus on the development of the targeting chemicals or compounds that are able to inhibit the activities of key proteins of the pathogens. For example, doxorubicin inhibits phosphatidylserine decarboxylase MoPsd2 and confers broad-spectrum antifungal activity, including *M. oryzae* (Zhou et al. 2023). Melatonin targets isocitrate lyase MoIcl1 and works synergistically with fungicide isoprothiolane to inhibit vegetative growth, conidial germination, appressorium formation, penetration, and infection of *M. oryzae* (Bi et al. 2023). Moreover, compound A378-0 and melatonin target the mitogen-activated protein kinase Mps1 and suppresses its enzyme activity to control rice blast disease (Li et al. 2023b; Kong et al. 2023). Additionally, three herbicides, metazachlor, cafenstrole, and diallate, were also reported to be effective drugs for rice blast disease control by targeting long-chain fatty acids biosynthesis pathway to block appressorium septin ring assembly (He et al. 2020). It is expected that a series of fungicides with novel targets in the pathogen will be developed soon.

Prospects

In the past decade, significant research progresses have been achieved to understand the mechanism of *M. oryzae*-rice interaction. During the long-term arms race with rice, *M. oryzae* have developed many effectors to suppress rice immune responses. Meanwhile, it continuously evolves specific races to evade rice immunity and to achieve successful infection. On the other hand, rice boosts the basal immune system-mediated PTI, and develops a more efficient and specific immune system-mediated ETI, to defend against the fungal infection. Identification of resistance genes in rice and avirulence genes in *M. oryzae* advances our understanding of *M. oryzae*-rice interaction at the molecular

level. Further studies are needed to better understand this interaction, likely in the following areas: (1) Identifying *M. oryzae* key receptors in recognizing rice cell surface signals and dissecting their function for appressorium formation; (2) Identifying and analyzing the functions of key proteins involved in appressorium formation and effector secretion using functional genomics, structural biology, and pesticide sciences; (3) Identifying broad-spectrum blast resistance genes in rice based on *M. oryzae*'s targets; (4) Investigating the evolution pattern of *M. oryzae* in the field with the help of the knowledge about *M. oryzae* population and biological data mining. These findings will not only contribute to explore potential fungicide targets and develop new fungicides of high efficiency and low toxicity, but also provide genetic basis for engineering of broad-spectrum blast resistance rice cultivars.

Abbreviations

Avr	Avirulence
BIC	Biotrophic interfacial complex
cAMP	Cyclic adenosine monophosphate
CFEM	Common in several fungal extracellular membrane protein
CWI	Cell wall integrity
COPII	Coat protein complex II
DDR	DNA damage-response
EIHM	Extra-invasive hyphal membrane
EMC	ER membrane protein complex
ER	Endoplasmic reticulum
EMC	ER membrane complex
ETI	Effector-triggered immunity
ETS	Effector-triggered susceptibility
GAP	GTPase-accelerating protein
GDP	Guanosine-5'-diphosphate
GEF	Guanylate exchange factor
GPCR	G-protein-coupled receptor
GTP	Guanosine triphosphate
HOG	High osmotic glycerol
HU	Hydroxyurea
LRR	Leucine-rich repeat
MAPK	Mitogen-activated protein kinase
MAX	*Magnaporthe* Avrs and ToxB-like
NBS	Nucleotide-binding site
NLR	Nucleotide-binding domain and leucine-rich repeat receptor
PAMP	Pathogen-associated molecular pattern
PKA	cAMP-dependent protein kinase A
PRRs	Pattern-recognition receptors
PTI	PAMP-triggered immunity
RGS	Regulator of G-protein signaling
ROS	Reactive oxygen species
SNARE	Soluble N-ethylmaleimide-sensitive-factor attachment protein receptor
TF	Transcription factor
TOR	Target of rapamycin
UPR	Unfolded protein response

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Author contributions
YLP and ZGZ conceived the concept. HFZ, JY, MXL, XZX, XYL, and LYY wrote the manuscript. YLP and ZGZ revised and finalized the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding authors on request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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