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# Metabolic Basis of Pathogenesis and Host Adaptation in Rice Blast

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## Keywords

autophagy, circadian, *Magnaporthe oryzae*, metabolism, phototropism, phytohormone, rice blast, ROS, reactive oxygen species

## Abstract

The blast disease, caused by the ascomycete *Magnaporthe oryzae*, poses a great threat to rice production worldwide. Increasing use of fungicides and/or blast-resistant varieties of rice (*Oryza sativa*) has proved to be ineffective in long-term control of blast disease under field conditions. To develop effective and durable resistance to blast, it is important to understand the cellular mechanisms underlying pathogenic development in *M. oryzae*. In this review, we summarize the latest research in phototropism, autophagy, nutrient and redox signaling, and intrinsic phytohormone mimics in *M. oryzae* for cellular and metabolic adaptation(s) during its interactions with the host plants.

## Contents



## 1. INTRODUCTION

*Magnaporthe oryzae* causes the most severe fungal disease, blast, in rice (*Oryza sativa*) and several other monocot crops (15, 84). During its pathogenic life cycle, *M. oryzae* produces asexual spores termed conidia that are formed in response to nutrient and phototropic signals and act as disease propagules under field conditions. A mature conidium is pyriform and composed of three cells, each containing a nucleus derived from a common mother nucleus. *M. oryzae* conidia are dispersed by air and act as key determinants of the spread and severity of blast disease. Upon landing on a suitable host surface, the conidium germinates and forms a dome-shaped infection structure named an appressorium at the tip of the germ tube. Within the appressorium, a very high turgor pressure is generated to facilitate the breach/penetration into the host cells. *M. oryzae* is a hemibiotroph, which implies that it does not kill the primary infected cells at the early stage of its *in planta* growth. When the invasive hyphae cross the host cell wall and spread to the neighboring cells, *M. oryzae* kills the primary infected cells by necrosis. *M. oryzae* initiates conidiation (conidia formation) again in the invasive hyphae to carry on its pathogenic life cycle and spread the blast disease (32).

During the infection process, *M. oryzae* encounters and responds to various environmental cues and biotic and abiotic stressors. For example, *M. oryzae* needs exposure to light for induction of asexual reproduction during mycelial growth. Under natural conditions, conidiation occurs at the site of infection, wherein *M. oryzae* likely faces severe nutrient limitation. During *in planta* growth, *M. oryzae* also experiences starvation and oxidative stress (imposed by host defense). Furthermore, rice plants produce various types of phytohormones as a defense mechanism against the fungal pathogen. To succeed in host infection and survive in such a complex environment, *M. oryzae* needs to constantly coevolve with and adapt to the host plants. Such fungal adaptation includes, but is not limited to, circadian biology (or phototropism), autophagy, integrated nutrient metabolism and redox homeostasis *in planta*, and the function of fungus-derived phytohormones. In this article, we review and discuss the latest studies on cellular adaptive strategies/mechanisms utilized by *M. oryzae* to precisely respond to the host environment in order to establish and propagate the devastating blast disease.

## 2. PHOTOTROPISM

Light is a ubiquitous environmental factor that influences many important biological processes. In fungal development, light serves several functions including phototropism, circadian rhythm, biosynthesis of carotenoids, asexual and/or sexual development, discharge of spores, etc. (23, 30, 31). Using *Neurospora crassa* as a model organism, key components of the biological circadian clock have been identified, and regulatory mechanism(s) unveiled (13, 24). The role of photobiology in fungal pathogenicity is just starting to be explored, with evidence showing that the conserved light-sensing White Collar Complex (WCC) components are critical for virulence of *Cryptococcus neoformans* (38) and *Fusarium oxysporum* (82). In this section, we discuss the latest advances in *M. oryzae* in the perception of light to initiate conidiation during pathogenic development while transiently suppressing disease progression. On the other hand, the host defense/resistance response against blast is also under circadian regulation.

### 2.1. Function of Light Sensor WC-1 in *M. oryzae*

The effect of light on asexual development has been studied in detail in *M. oryzae* (48). It has been shown that the light/dark cycle is essential for *M. oryzae* asexual development; the dark phase is required for aerial hyphae formation and for spore release, while light exposure enables conidia formation. Furthermore, the ortholog of *N. crassa WC-1*, encoding a blue light receptor, was identified in *M. oryzae* and was deleted to study the role of blue light (470 nm) in asexual development in the blast fungus. The result showed that *MoWC-1* is involved in the light-dependent release of asexual spores (48) but does not regulate the biogenesis/formation of such spores (conidia) in *M. oryzae*.

On the other hand, the function of *MoWC-1* was also studied in disease development (45). The blue light receptor MoWc-1 was shown to be responsible for sensing darkness immediately after pathogen-host contact, as a prerequisite for disease development. Failing to do so results in light-based suppression of blast disease, even during the compatible interaction between the pathogen and host. A genome-wide microarray experiment was performed, and several gene families that are differentially regulated during the light-to-dark transition were identified. The top two enriched differentially regulated gene families are related to melanin/pigment biosynthesis and nucleotide binding, suggesting a metabolic adaptive mechanism during the light-to-dark switch dependent on the MoWc-1 associated phototransduction pathway.

The core circadian clock components, Frq (Frequency) and WCC, are conserved in several filamentous fungi including *M. oryzae* (58), suggesting an Frq-based oscillator in these organisms. However, so far there has been no report on Frq function in *M. oryzae* development or pathogenicity; only the *MoFRQ* transcript has been shown to be induced by light exposure in a MoWc-1-dependent manner (19, 45). Besides the blue light receptor Wc-1, or WCC in *M. oryzae*, several other light sensors are also predicted based on sequence similarity in the *M. oryzae* genome (**Table 1**). Among them, the predicted red light sensor phytochrome-1, encoded by *MGG_12377*, was reported to encode a histidine kinase (HK), but the loss of this gene caused no obvious phenotypic defects (39). On the other hand, the transcriptional repressor Tup1 plays an important regulatory role in *M. oryzae* growth, development, and pathogenesis (14) and shows sequence similarity to the UV sensor Cop1 in *A. thaliana*. Detailed functional investigation is lacking for the other predicted *M. oryzae* light-sensor-encoding genes. We believe that investigation of these predicted light-sensor-encoding genes and of *MoFRQ* gene function, as well as their relationship and cross talk, would provide more information as to how *M. oryzae* perceives ambient light and makes cellular/metabolic adjustments or morphological changes as a response, in order to cope with adverse environments and/or to take full advantage of the favorable phototropic environment.

**Table 1 Genes involved in photomorphogenesis in *Magnaporthe oryzae***

| Gene ID and annotation (*Magnaporthe oryzae*)[a] | Functionally characterized orthologs | | | Light |
|---|---|---|---|---|
| | *Arabidopsis thaliana* | *Aspergillus nidulans* | *Neurospora crassa* | |
| *MGG_12377*, phytochrome-1 (39) | *PhyB/PhyA* | *FphA* | *Phy-1/Phy-2* | Red/far-red |
| *MGG_00190* | *PIF3* | Not reported | Not reported | Red/far-red |
| *MGG_00408*, *MGG_13576*, (RCC1 domain) | *UVR8* | Not reported | Not reported | UV |
| *MGG_08829*, Tup1 (14) | *COP1* | Not reported | *RCO-1* | UV, red, far-red, blue |
| *MGG_02071*, cryptochrome-1 | *CRY2* | Not reported | *PHR* | Blue |
| *MGG_06836*, deoxyribodipyrimidine photolyase | *CRY2* | Not reported | *PHR* | Blue |
| *MGG_00190* | *CIB1* | Not reported | Not reported | Blue |
| *MGG_03538*, White Collar 1 (45, 48) | No ortholog | *LreA* | *WC-1* | Blue |
| *MGG_04521*, White Collar 2 | No ortholog | *LreB* | *WC-2* | Blue |
| *MGG_01041*, Envoy (PAS/LOV motif) | Multiple PAS/LOV motif-encoding genes | No ortholog | *VVD* | Blue |

[a]The orthologs for photomorphogenesis genes in *M. oryzae* were identified using **https://blast.ncbi.nlm.nih.gov/Blast.cgi** or **http://fungi.ensembl.org/Magnaporthe_oryzae/Tools/Blast?db=core**.

## 2.2. Cell Signaling Associated with Phototropism in Rice Blast

It remains largely unknown how *M. oryzae* relays the light signal into the intracellular machinery. Deng et al. (19) identified a circadian-regulated gene whose transcript specifically peaks at subjective dawn (before sunrise) in the circadian cycle; it is therefore named *TWILIGHT* (*TWL*) (**Figure 1**). *TWL* is required for proper conidiation and pathogenicity in *M. oryzae*. Interestingly, the conidiation defect in the *twl*Δ mutant could be restored by exogenous supplementation with rice extracts, in a dose- and light-dependent manner. On the other hand, the infection defect in the *twl*Δ mutant could be suppressed by addition of the antioxidant glutathione (GSH). These results indicate that Twl may serve as an integrator of metabolic and redox homeostasis with phototropism during fungal development. In further support of this hypothesis, the Twl protein is phosphorylated by Snf1, a nutrient-sensing kinase, in response to light exposure (**Figure 1**). Mutually exclusive modification of Twl, by phosphorylation or acetylation, alternates during dark-light cycles, making Twl shuttle between the nucleus and cytosol. Nuclear Twl contributes to induced expression of the transcription factor Tfb5, which in turn promotes conidiation in response to light (19).

Besides Twl and Tfb5, a histone acetyltransferase (HAT), Gcn5, was identified to be light regulated as well (113) (**Figure 1**). Further investigation revealed that Gcn5 function is pleiotropic, and it shuttles between the nucleus and the cytosol. In the dark, the level of *GCN5* transcript is low, and the Gcn5 protein is mainly cytosolic and is involved in suppression of autophagy via Atg7 acetylation. Light induces the transcription of *GCN5* and triggers transport of Gcn5 protein into the nucleus, which relieves the suppression of autophagy and consequently induces the expression of genes in favor of *M. oryzae* conidiation (113). As autophagy serves a nutrient catabolism function essential for conidiation (see Section 3.1), such phototropic induction of glycogen autophagy [(a selective form of autophagy for glycogen hydrolysis and degradation (46)] (**Figure 1**) represents another example of a specific cellular adaptive mechanism in *M. oryzae* in response to environmental cues such as light and nutrition.

Two-component signal transduction (TCST) pathways play crucial roles in stress responses, biofilm formation, and sporulation in microbes (49, 73). Typically, such pathways involve a

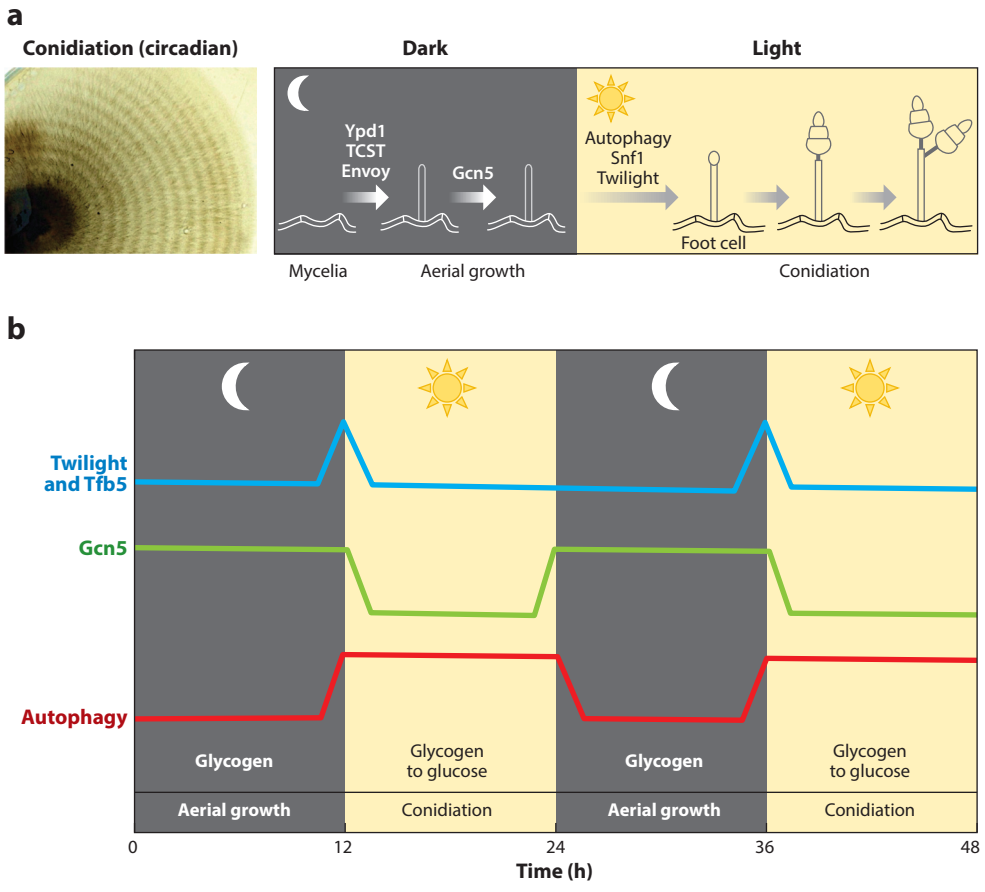


**Figure 1**

Rhythmic production of conidia (asexual spores) is regulated by the phototropic/circadian response and nutrient homeostasis in *M. oryzae*. (*a*) Axenic cultured *M. oryzae* shows a mycelial banding pattern during dark/light cycles that represents successive rounds of aerial hyphal growth (in the dark) and conidiation (under light). The histidine phosphotransferase Ypd1 regulates aerial hyphal growth, likely via TCST-based transcriptional induction of the Envoy gene, which encodes a putative light sensor. The histone acetyltransferase Gcn5 mediates proper aerial growth and prevents precocious conidiation in the dark. Autophagy, Snf1 kinase, and Twilight are key modulators of nutrient homeostasis and conidiation in response to phototropism in *M. oryzae*. (*b*) Functions of Twilight, Tfb5, Gcn5, and autophagy show highly coordinated rhythmic oscillations in the two differential phases of such diurnal cycles. The schematic in panel *a* is adapted in part from Reference 20 under a Creative Commons attribution-noncommercial license. Abbreviations: Gcn5, general control nonderepressible 1; Snf1, sucrose nonfermenting 1; TCST, two-component signal transduction; Ypd1, tyrosine phosphatase dependent 1.

transmembrane HK for sensing external signal(s) and a response regulator (RR) for activation of the downstream mitogen-activated protein kinase (MAPK) cascade or for direct transcriptional regulation of the target genes. The histidine phosphotransferase (HPt) is an intermediate phosphotransfer protein that acts as an important mediator between the upstream sensor HK and downstream RR. The *M. oryzae* genome has ten HKs, one HPt, and three RRs, predicted to be involved in various stress responses, morphogenesis, growth, and development (39, 66, 67, 112). An HPt gene, *YPD1*, was identified in *M. oryzae* and displayed light-induced expression.

Furthermore, Ypd1 was found to be essential for activation of TCST-dependent MAPKs, as well as photoinduction of the PAS/LOV domain–containing Envoy protein (predicted light sensor, **Table 1**; **Figure 1**) or most of the PAS-domain HKs, to regulate diverse light-responsive functions in *M. oryzae*, including aerial hyphal growth during conidiation (**Figure 1**) and oxidative stress tolerance during host invasion (65).

At present, our understanding of the phototransduction pathways in *M. oryzae* is unsystematic and far from complete. Further investigations are required to elucidate the epistatic relationship between these light-sensing and/or -responsive components, and eventually to construct a cellular signaling network that encompasses phototropic regulation of nutrient and redox homeostasis essential for fungal pathogenicity.

### 2.3. Circadian Rhythm and Blast Resistance

From an evolutionary point of view, the ability of fungal pathogens to perceive and respond to light and/or the circadian cycle imparts to them an advantage in this host-pathogen arms race. Similarly, the circadian cycle also seems to play a role in shaping the expression patterns of the genes associated with plant immunity. Circadian regulation of plant metabolism, growth, and development has been shown, and the molecular mechanism underlying the circadian clock in plants has been elucidated using *Arabidopsis thaliana* as a model system (63, 69). More recently, several studies have demonstrated circadian regulation of plant immunity, including the dark-light-oscillations in salicylic acid (SA) and jasmonic acid (JA) signaling (86, 88, 102, 115), and/or redox signaling (43, 93). Generally, plant defense against microbial pathogens is more active during daytime and remains suppressed in the night, as suggested by the aforementioned research studies and/or review articles. Therefore, the fungal pathogen that has evolved to invade the host at night likely encounters less resistance and thus has better chances of survival *in planta*. On the other hand, the fungal mycelia that have successfully invaded during the dark phase may conidiate *in planta* in the following daytime, using photo exposure as a signaling trigger; and they use such newly formed conidia as propagules for the subsequent round of blast invasion (again at night).

Unlike the case of *A. thaliana*, reports on circadian regulation of disease resistance (including against blast) in rice are very limited. Two rice ascorbate peroxidase (*OsAPX1* and *OsAPX2*) genes are induced by various stresses including *M. oryzae* attack, but strongly in the light compared to the dark. Moreover, *OsAPX1/2* mRNA expression manifested a clear rhythm under a light/dark cycle (1). This study, along with another report on light-induced expression of rice defense genes *OsPR1a* and *OsPR1b* in response to *M. oryzae* infection (2), suggests diurnal regulation of blast resistance in the host. Besides, a *GT-1*-like transcription factor was found to oscillate in dark/light cycles, induced by *M. oryzae* and suppressed by light (101), but its role in plant-pathogen interaction awaits further investigation. A conserved eukaryotic release factor 1 protein encoded by the rice *LML1* gene was found to regulate programmed cell death in a light-dependent manner and is predicted to act as a negative regulator of blast resistance, likely through transcriptional suppression of the defense genes *PR1*, *PBZ1*, *NAC*, *PAL1*, and *PR10* (79). Overall the studies on light/dark rhythmic regulation of rice resistance against blast disease (and other microbial pathogens) have just been initiated but are of great interest, as they will broaden our understanding of plant resistance and fungal pathogenicity in the context of circadian input and adaptation.

## 3. NUTRIENT HOMEOSTASIS DURING FUNGAL DEVELOPMENT

Nutrition availability is another important environmental factor influencing many stages of fungal development. Generally, fungal pathogens are predicted to experience nutrient limitation during

the early stages of invasive growth, especially for hemibiotrophic fungi before necrosis of the host cell is induced. Autophagic degradation of fungal cell storage of macromolecules, including polysaccharides or lipids, may be a common strategy to cope with such starvation during fungal *in planta* growth.

### 3.1. Autophagy Acts as a Starvation Response and an Active Executor of Developmental Cell Death

Autophagy is a vacuole-based, multistep process of bulk degradation or regulated turnover of cytoplasmic components and organelles in eukaryotes. Based on different morphology and on a molecular basis, autophagy can be classified into three forms: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) (75). These can be further classified into selective forms of autophagy such as mitophagy (autophagic degradation of mitochondria), pexophagy (selective autophagy of peroxisomes), and ERphagy (selective autophagy of endoplasmic reticulum) (46).

As a cellular adaptive mechanism, autophagy is induced during several biological processes, including in response to environmental stress or pathogen invasion, and cellular remodeling during development and differentiation (46). Using budding yeast *Saccharomyces cerevisiae* or animal cells as model systems, researchers have elucidated genetic and molecular regulation of macroautophagy, with 42 *ATG* (*AuTophaGy*) proteins identified and characterized thus far (74). On the other hand, CMA involves recognition of a specific set of cytoplasmic substrates/proteins by a chaperone complex, and translocation of such CMA substrates into a lysosome with the assistance of a specific lysosomal receptor (11). Molecular machinery for microautophagy, however, has not been explored in detail (50). A number of *ATG* genes required for macroautophagy also contribute to microautophagy (50). Among all these *ATG* genes, *ATG8* has been established as a marker for macroautophagy induction and autophagy-associated vesicular compartments such as autophagosomes and autophagic vacuoles (42). Hereafter, we use the term autophagy to denote nonselective macroautophagy, unless otherwise stated.

Investigations in autophagy function in *M. oryzae* started more than a decade ago. Thus far, orthologs of 25 *ATG* genes have been identified in *M. oryzae*, 11 of which were characterized by reverse genetics (**Table 2**). Such studies have revealed pleiotropic function(s) of autophagy in conidiation and infection in rice blast. The first report of autophagy in *M. oryzae* came from the Talbot group, demonstrating that autophagy facilitates highly specific conidial cell death to ensure maturation and proper function of appressoria (96). Shortly thereafter, autophagy was found to serve an important function in maintaining homeostasis of lipid bodies during appressorium formation and maturation (56). While these two studies focused on autophagy function during the infection process in *M. oryzae*, another important aspect, i.e., conidiation/asexual development, was also reported to be dependent on autophagy. Deng et al. investigated the cellular function(s) of autophagy during *M. oryzae* conidiation and found that autophagy is essential for (*a*) maintaining redox homeostasis therein, and (*b*) bulk hydrolysis of cytosolic stored glycogen, a process mirroring glycogen autophagy in mammalian cells, during asexual development in the blast fungus (17, 20).

Besides bulk autophagy, selective forms of autophagy have also been investigated in *M. oryzae*. Mitophagy was shown to occur in specialized structures called foot cells, and it was found to be essential for conidiation (35) and pathogenicity (116). In contrast, pexophagy was found to be dispensable for *M. oryzae* pathogenicity (16).

These studies demonstrated that autophagy plays pleiotropic roles in *M. oryzae* pathogenicity, including macromolecule (polysaccharide, lipid, etc.) and/or organellar (mitochondrion, peroxisome) homeostasis, and autophagic cell death. Considering the adverse environment that

**Table 2 Identified and characterized *AuTophaGy* genes in *Magnaporthe oryzae***

| Gene[a] | Gene ID[b] in *M. oryzae* | References |
|---|---|---|
| *ATG1* | *MGG_06393* | 56 |
| *ATG2* | *MGG_05998* | 44, 55 |
| *ATG3* | *MGG_02959* | 44 |
| *ATG4* | *MGG_03580* | 44, 54, 55 |
| *ATG5* | *MGG_09262* | 44, 55, 60 |
| *ATG6* | *MGG_03694* | 44 |
| *ATG7* | *MGG_07297* | 44, 113 |
| *ATG8* | *MGG_01062* | 20, 44, 55, 96 |
| *ATG9* | *MGG_09559* | 21, 44, 55 |
| *ATG10* | *MGG_14737* | 44 |
| *ATG11* | *MGG_04486* | 44 |
| *ATG12* | *MGG_00598* | 44 |
| *ATG13* | *MGG_00454* | 44 |
| *ATG14* | *MGG_03698* | 57 |
| *ATG15* | *MGG_12828* | 44 |
| *ATG16* | *MGG_05255* | 44 |
| *ATG17* | *MGG_07667* | 44 |
| *ATG18* | *MGG_03139* | 44, 55 |
| *ATG20/SNX42* | *MGG_12832* | 16 |
| *ATG22* | *MGG_09904* | 44 |
| *ATG24* | *MGG_03638* | 35, 44 |
| *ATG26* | *MGG_03459* | 16, 44 |
| *ATG27* | *MGG_02386* | 44 |
| *ATG28* | *MGG_08061* | 44 |
| *ATG29* | *MGG_02790* | 44 |

[a]Source of information for autophagy genes: **http://yeastgenome.org**.
[b]The orthologs for *ATG* genes in *M. oryzae* were identified using **https://blast.ncbi.nlm.nih.gov/Blast.cgi** or **http://fungi.ensembl.org/Magnaporthe_oryzae/Tools/Blast?db=core**.

a pathogen encounters during its infection/invasive growth stage, we could view autophagy as a strategy adopted by the pathogen to survive such stressful conditions. Autophagy-assisted glycogen hydrolysis could cope with a sudden demand for ample energy or cellular buildup of substrates, to fulfill the metabolic requirements during morphogenesis, especially *in planta*, wherein exogenous sources of nutrients are expected to be limited. On the other hand, autophagy assists cell death in conidia upon appressorium formation, with such cell death serving as a prerequisite for subsequent appressorium-mediated host invasion. Thus, autophagy serves prosurvival and prodeath functions in *M. oryzae*.

Further investigation is needed toward understanding the physiological and environmental cues that induce autophagy in *M. oryzae* at different pathogenic stages. In a recent report, autophagy induction during *M. oryzae* conidiation was shown to be not just a passive response to starvation but rather an active induction that occurs in response to light. Phototropism-based induction of autophagy required the removal of Gcn5-catalyzed acetylation of the autophagy protein Atg7 (113). Further analysis revealed that Gcn5-mediated suppression of autophagy in the dark is cooperatively achieved by epigenetic modification of histone H3 protein and (cytosolic) autophagy protein Atg7 (51). Recently, more reports have collectively revealed that protein acetylation and

deacetylation cycles catalyzed by HATs and histone deacetylases (HDACs), respectively, play a role in regulating autophagy and fungal pathogenicity (34, 47, 62). HATs and HDACs may serve as a connection between autophagy and physiological and/or environmental inducers. We believe that a more detailed mechanistic basis of fungal adaptation to the environment would be revealed through identification of protein substrates of HATs or HDACs, and investigation of their biological function. Therefore, two recent reports on identification of a substantial number of acetylated proteins (51, 94) provide a promising list of candidates for such studies in the future. Furthermore, it will be of great interest to identify the inducer(s) of autophagy responsible for conidial cell death during appressorial development. A possibility could be the role of reactive oxygen species (ROS) generated by the host upon pathogen recognition, and induced as part of the defense response.

### 3.2. Nutrient Acquisition and Utilization *In Planta*

In the context of nutrient acquisition and utilization during progressive *M. oryzae* infection, an integration of carbon and nitrogen metabolism by trehalose-6-phosphate synthase 1 (Tps1) has been studied extensively (26, 28, 105). Multiple glycogen metabolism genes have also been shown to be important for *M. oryzae* pathogenicity, since they are required for transcriptional regulation of genes encoding components of the trehalose-6-phosphate synthase complex; this includes *TPS1* (8). Thus, Tps1 was proposed as a molecular target for drug design for control of rice blast disease (106).

In the last section, we discussed the ability of *M. oryzae* to hydrolyze and recycle cytosolic glycogen, to produce glucose (as a preferred carbon source) for its cellular buildup and/or as an energy requirement. Another strategy that a pathogenic fungus could utilize to produce sufficient glucose may be via hydrolysis of sucrose within plant tissue by a high-affinity invertase. Such a high-affinity invertase contributing to fungal virulence was first identified in the corn smut fungus *Ustilago maydis* (98). Recently, a secreted invertase was shown to serve a similar function in nutrient exploitation in *M. oryzae*, during host-pathogen interaction (52). Moreover, as this *M. oryzae* invertase Inv1 is a secreted protein, it could also be viewed as a cooperative trait or public goods in the population, fitting into the cooperation theory/model. The cooperation theory predicts that the presence of public goods cheaters, in this case the *M. oryzae* mutant not producing a functional Inv1 enzyme and thus showing low virulence, leads to a reduction in overall virulence of the population. However, mixed infection with the conidia of a less virulent *INV1* mutant and wild type (highly virulent) leads to an increase in the damage to the host and induces production of new conidia, also containing both producer and nonproducer strains (52). This observation could be explained in terms of the low efficiency of sucrose utilization by the *INV1* wild-type population being alleviated by the mixed *inv1* mutant, likely by reducing the local sucrose concentration. A mixture of public goods cooperators and cheaters could maximize microbial fitness and virulence of the population, which needs to be considered when forming disease control strategies. This example also indicates that a density-dependent determinant of host damage likely exists in *M. oryzae* and is involved in monitoring local nutrient limitation or availability.

## 4. REDOX HOMEOSTASIS

Plants dynamically perceive and respond to environmental stimuli, including pathogen invasion. Plant defense response usually involves a rapid increase in the levels of ROS at the infection site (5, 86). On the other hand, plant pathogens have evolved the ability to detoxify such plant-derived ROS in order to ensure successful infection (4). In this section, we discuss two metabolic

intermediates, NAPDH and GSH, as potent antioxidants and their important function(s) in *M. oryzae* infection and host damage.

As mentioned in Section 3.2, the metabolic enzyme Tps1 could act as a monitor of cellular glucose 6-phosphate levels and a regulator of gene expression integrating metabolic status. It has been further found that the metabolic intermediate and antioxidant NADPH could also directly bind to Tps1 and regulate its transcriptional activity (104). On the other hand, NADPH-oxidase-encoding genes *NOX1* and *NOX2* were shown to be essential for septin ring organization at the appressorium pore (where a penetration peg later develops), which likely depends on ROS production from the fungal side (25, 83). It remains unclear whether NADPH is secreted by the blast fungus, as an antioxidant strategy against the host defense response centered on ROS burst.

Glutathione is a simple sulfur compound composed of three amino acids, glutamate, cysteine, and glycine, serving a function in redox-homeostatic buffering in organisms, including pathogenic fungi. Glutathione is synthesized through a metabolic pathway named the γ-glutamyl cycle; and it can be converted from oxidized and reduced forms, GSSG and GSH, respectively. A glutathione antioxidant system was shown to contribute to resistance toward host ROS challenge and successful infection (27, 85).

We identified a sorting nexin essential for conidiation and invasive growth in *M. oryzae* (18). This sorting nexin (named MoSnx41) was found to be similar to the yeast Snx41 and Snx42 in amino acid sequence and shown to serve a dual function in pexophagy and endosomal sorting. Further investigation revealed that MoSnx41 mediates sorting and retention of a critical enzyme, Oxp1, in amino acid biogenesis and GSH metabolism through the γ-glutamyl cycle, which produces glutathione as an intermediate product. Therefore, Snx41-mediated endosomal sorting of Oxp1 plays a pivotal role in suppression of host ROS burst during the initial stages of rice blast (18). Interestingly, NADPH-dependent Tps1 regulation is required for the expression of the *GTR1* gene, encoding a glutathione reductase that converts an oxidized form of glutathione disulfide (GSSG) to the reduced variant (GSH), especially during the *in planta* stage (27). This connects biosynthesis and redox turnover of these two antioxidants in *M. oryzae* pathogenicity.

It was proposed that *M. oryzae* experiences and requires dynamic redox oscillation during its infection process, which is tightly regulated through NADPH-dependent metabolic and/or genetic reprogramming. Overall, we summarize a working model (**Figure 2**) displaying an integrative view of *M. oryzae* metabolic and redox homeostasis with regulation by membrane trafficking, including autophagy and endosomal sorting, in *M. oryzae*.

## 5. THE RELEVANCE OF *M. ORYZAE*–DERIVED PHYTOHORMONES TO METABOLIC REGULATION

In the highly competitive plant-microbe relationships, phytohormones serve as one of the most important host defense mechanisms against pathogen invasion (78, 87, 108). Currently, eight types of phytohormones have been well established: abscisic acid (ABA) (33), auxins [indole-3-acetic acid (IAA)] (6, 7), brassinosteroids (BRs) (72), cytokinins (CKs) (41), ethylene (ET) (10), gibberellins (GAs) (91), JAs (103), and SA (9). Their physiological roles in plant growth, development, and abiotic and biotic stress resistance have been well documented. Involvement of phytohormones in plant immunity has been extensively investigated using *A. thaliana* (59, 81, 97, 103) and rice (22, 36, 37, 53, 61, 64, 70, 80, 90, 100, 107, 109, 111). Here, we briefly discuss plant immunity functions of phytohormones, with greater emphasis on recent research revealing the novel role(s) of *M. oryzae*–derived phytohormone mimics in metabolic regulation of infection and immunity in rice.

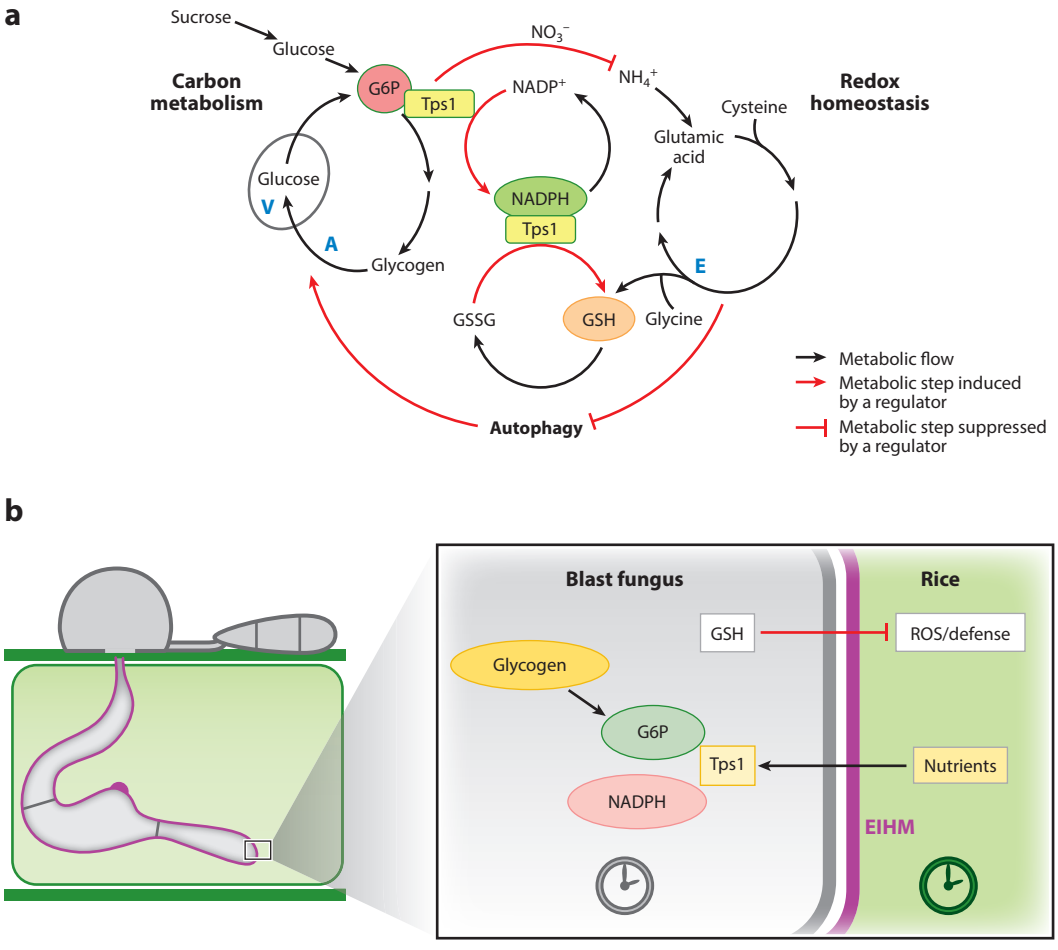


**Figure 2**

Metabolic and redox homeostasis mediated by vesicular trafficking at the fungus-host interface in rice blast. (*a*) Intracellular glucose, derived from hydrolysis of extraneous sucrose catalyzed by *M. oryzae* invertase, or generated via glycogen autophagy (which is suppressed by the presence of a readily usable carbon source), is likely phosphorylated to glucose 6-phosphate. Tps1 acts not only as a metabolic enzyme but also as a central regulator of carbon metabolism (pentose phosphate pathway) and intracellular levels of NADPH. Amino acid metabolism via the γ-glutamyl cycle produces GSH as an intermediate product that is maintained in fungal cytosol by Snx41-mediated endosomal sorting. Both NADPH and GSH are utilized by the blast pathogen for suppression of host defense response involving the ROS burst. Membrane-bound compartments (*blue*) are denoted as follows: A, autophagosome; E, endosome; V, vacuole. Panel *b* shows a simplified model focusing on nutrient- and redox-based communication between rice and *M. oryzae*, both of which are subject to circadian regulation and are likely in sync. Abbreviations: EIHM, extra invasive hyphal membrane; G6P, glucose 6-phosphate; GSH, reduced glutathione; GSSG, oxidized glutathione; $NADP^+$, oxidized form of NADP; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); ROS, reactive oxygen species; Tps1, trehalose-6-phosphate synthase.

## 5.1. Phytohormone Mimics Produced by the Blast Fungus

*M. oryzae* infection can alter phytohormone production in rice, as reported for auxin-responsive genes *ARF1* and *IAA9*, which are downregulated in distal uninfected rice leaves, away from the site of initial pathogen attack, thus inducing the systemic acquired resistance (SAR) to restrict the spread of blast disease (40). Blast infection also triggers CK accumulation in the rice seedlings, and

CK-mediated blast resistance, which is likely synergistically regulated by an SA signaling pathway (41). It appears that IAA plays a negative, while CKs play a positive, role in rice SAR against *M. oryzae* infection. On the other hand, ABA in plants may suppress SAR mediated by SA, JA, and ET signaling pathways (3, 68, 95). Therefore, reduction of ABA production or disruption of ABA signaling in rice enhances resistance to blast disease (110), while ABA treatment of rice seedlings resulted in susceptibility toward incompatible and compatible *M. oryzae* isolates (40). *M. oryzae* was able to stimulate host ABA synthesis, likely by upregulating the rice *NCED3* transcript, to facilitate its own pathogenicity and to subvert host resistance (92).

Besides altering phytohormone production in the host plant to suppress the defense response, *M. oryzae* produces IAA, CKs, and ABA in its hyphae and conidia (41, 89) and likely secretes them (12) as potential virulence factors. Biosynthesis pathways for these three phytohormones remain largely unknown in *M. oryzae*, except for a *CKS1* gene encoding a putative tRNA-IPT protein essential for CK biosynthesis (12), and three *ABA* biosynthesis genes (*MoABA1*, *MoABA2*, and *MoABA4*) (92) that were identified and characterized. It is intriguing that *M. oryzae* produces and secretes CK, which activates the host defense response, seemingly in opposition to its own infection. Current studies suggest that CKs may facilitate nutrient (sugars and key amino acids) translocation for the blast fungus (12, 99), thus serving an essential physiological/metabolic function. Overall, *M. oryzae* is able to manipulate host production of and/or response to phytohormones IAA, CKs, and ABA or to produce these three signaling molecules. This represents a unique interkingdom chemical communication between a pathogenic fungus and its plant host that determines the severity of blast disease.

### 5.2. Phytohormones Modified by *M. oryzae*: Jasmonic Acid

*M. oryzae* is able to manipulate the JA signaling pathway in rice and thus defeat host defense. *M. oryzae* specifically induces the expression of rice miR319, whose target gene encodes the transcription factor OsTCP21, which positively regulates rice defense response against the blast disease, likely via inducing JA synthesis genes *LOX2* and *LOX5* (114). Therefore, *M. oryzae* is able to suppress JA synthesis and JA-mediated defense in rice.

Antibiotic biosynthesis monooxygenase (Abm) in *M. oryzae* hydroxylates endogenous free JA to 12OH-JA. The fungus-derived 12OH-JA is secreted during host penetration and helps evade the defense response by suppressing JA signaling in the host tissue. Loss of Abm in *M. oryzae* leads to accumulation of methyl JA (MeJA), which induces a novel form of host defense and blocks invasive growth (76). It appears that *M. oryzae* secretes Abm into the host plants, likely to convert the plant JA into 12OH-JA and facilitate host colonization (77).

In this section, we reviewed the phytohormones simulated or modified by *M. oryzae* to suppress the host defense. However, studies on such fungus-derived phytohormones are preliminary, and further investigation into their biosynthesis, regulation, signaling, and physiological function(s) is eagerly awaited.

## 6. PERSPECTIVES

We reviewed the recent advances in *M. oryzae* biology underlying its pathogenicity, particularly an integrative metabolic adaptation consisting of carbon, nitrogen, and redox homeostasis, likely entrained by circadian rhythm/phototropism and other environmental cues, toward fungal differentiation and pathogenicity (**Figure 3**). *M. oryzae* is also able to produce and likely secrete small molecules simulating phytohormones, or even to directly modify one or more host phytohormones as a strategy for disease establishment. Such an ability may also be subject to circadian

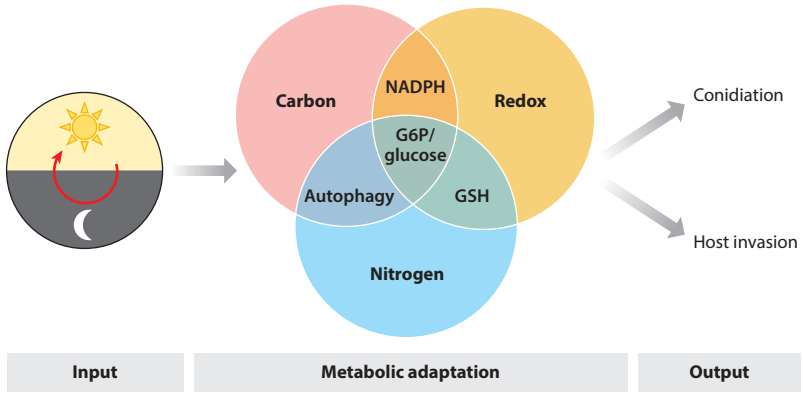


**Figure 3**

An integrated view of the metabolic adaptation during pathogenesis in *M. oryzae*. *M. oryzae* senses environmental signals, including light, and uses them as input to adjust its own cellular metabolism. Fungal pathogenicity, two important aspects of which are conidia formation and host invasion, is the output of such metabolic adaptation in response to external cues. Overlap between different metabolic categories represents coregulation and/or functional interconnectedness. Abbreviations: G6P, glucose 6-phosphate; GSH, reduced glutathione; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form).

regulation/phototropism, as well as metabolic and/or redox inputs, as reported for *A. thaliana* (29, 71), but this remains to be characterized in the rice blast pathosystem. Although we discussed each aspect individually, they do not necessarily function independent of each other. Instead, complex interconnections are expected between circadian rhythm/phototropism, metabolic and redox homeostasis, and phytohormone signaling in the blast fungus. Further elucidation of such complex metabolic networks will be required for a proper holistic understanding and control of the blast disease in rice and other important cereal crops.

## SUMMARY POINTS

1. The blast fungus, *Magnaporthe oryzae*, senses and responds to light as a major input to modulate its cellular metabolism.
2. Nutrient- and redox-based signaling between rice (*Oryza sativa*) and *M. oryzae* is subject to circadian regulation via autophagy.
3. *M. oryzae* likely syncs its clock with that of the host via specific nutrient(s) perceived during biotrophic growth.
4. *M. oryzae* secretes small molecules that simulate phytohormones, or directly modify host phytohormone(s), as a strategy for disease establishment.
5. *M. oryzae*–derived phytohormone mimics may be subject to circadian regulation as well as metabolic and/or redox input.

## FUTURE ISSUES

1. A detailed functional investigation on the predicted light sensor and the master regulator Frequency, as well as their relationship and cross talk, will help us better understand

how *M. oryzae* perceives ambient light and makes cellular/metabolic adjustments or morphological changes as a response to cope with adverse environments and/or to take full advantage of the favorable phototropic environment in the host plants.

2. The epistatic relationship between these light-sensing and/or response regulators is required for a systematic and complete understanding of the phototransduction pathways in *M. oryzae*.
3. A more comprehensive understanding of plant immunity and fungal pathogenicity in the context of circadian regulation and metabolic adaptation will help in designing novel strategies for control of blast disease.
4. Understanding the physiological and environmental cues that induce autophagy in *M. oryzae* and rice will provide insight into key steps involved in establishment and spread of blast disease.
5. Future studies will help identify whether a density-dependent (quorum-sensing) determinant of host damage exists in the rice blast pathosystem.
6. Identification of biosynthesis, transport, signaling, and physiological function(s) of *M. oryzae*–derived phytohormone signatures will be crucial in understanding the role of such metabolites in fungal pathogenesis and blast disease progression.

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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