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MINI-REVIEW

Response and regulatory mechanisms of heat resistance in pathogenic fungi

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Abstract

Both the increasing environmental temperature in nature and the defensive body temperature response to pathogenic fungi during mammalian infection cause heat stress during the fungal existence, reproduction, and pathogenic infection. To adapt and respond to the changing environment, fungi initiate a series of actions through a perfect thermal response system, conservative signaling pathways, corresponding transcriptional regulatory system, corresponding physiological and biochemical processes, and phenotypic changes. However, until now, accurate response and regulatory mechanisms have remained a challenge. Additionally, at present, the latest research progress on the heat resistance mechanism of pathogenic fungi has not been summarized. In this review, recent research investigating temperature sensing, transcriptional regulation, and physiological, biochemical, and morphological responses of fungi in response to heat stress is discussed. Moreover, the specificity thermal adaptation mechanism of pathogenic fungi in vivo is highlighted. These data will provide valuable knowledge to further understand the fungal heat adaptation and response mechanism, especially in pathogenic heat-resistant fungi.

Key points

- *Mechanisms of fungal perception of heat pressure are reviewed.*
- *The regulatory mechanism of fungal resistance to heat stress is discussed.*
- *The thermal adaptation mechanism of pathogenic fungi in the human body is highlighted.*

Keywords Fungi · Heat sensing · Heat adaptation · Molecular mechanisms · Heat shock transcription factors

Introduction

Mammalian body temperature can serve as a nonspecific defense against invasive fungal diseases; most fungi cannot grow at this temperature (Bergman and Casadevall 2010; Robert and Casadevall 2009). The mammalian immune system also plays an important role in fungal infection. However, the number of critically ill patients with cancer, chronic disease, or coronavirus disease 2019 (COVID-19) has increased over recent years while immune function has decreased, increasing susceptibility to fungal diseases. At present, the occurrence of thermophilic and heat-resistant fungi has also increased the risk of fungal infections in humans. In the COVID-19 burst period, due to infection with *Aspergillus* strains, SARS-CoV-2-associated pulmonary aspergillosis was a major, life-threatening fungal disease in these patients (Hoenigl 2021; Salmanton-Garcia et al. 2021). In addition, the global outbreak of *Candida auris*, a new heat-resistant pathogenic fungus, has attracted attention because of its high-temperature resistance, multiple

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drug resistance, and high fatality rate (Spivak and Hanson 2018). *C. auris* infection may be the first case of a new fungal disease caused by global warming (Casadevall et al. 2019). Although there is no direct evidence confirming the correlation between global warming and heat-resistant fungi, the study of fungal heat adaptation mechanisms can help our understanding of how heat-resistant fungi emerge. These investigations would also suggest solutions to prevent more heat-resistant fungal infections in the future.

Each fungus has an optimal temperature for survival. Severe ambient temperature can cause damage, including misfolded proteins, accumulation of oxidative stress caused by reactive oxygen species (ROS), and osmotic stress caused by osmotic pressure changes (Gao et al. 2016; Moraitis and Curran 2004). Fungi also have a series of complex regulatory systems to cope with the damage. Therefore, fungi can adapt to high-temperature changes, maintaining their existence and reproduction under the condition of temperature fluctuations. These adaptive mechanisms include heat shock transcription factors (HSFs) to regulate activation of conservative signaling pathways, antioxidant responses, heat shock (HS) responses, and trehalose accumulation (Sugiyama et al. 2000a; Zahringer et al. 2000). To improve the economic benefit in industrial production, the heat resistance mechanism of *Saccharomyces cerevisiae* has been a major mainly focus (Thorwall et al. 2020). In recent years, due to the aggravation of fungal pathogenic diseases in humans, research on thermal adaptation mechanisms of pathogenic fungi has been increasing. However, few articles summarized recent advances in the study of heat resistance in pathogenic fungi. In this review, we summarize the recent research progress of different fungal heat adaptation mechanisms and confirm that heat shock, an ancient response, is highly conserved in fungal organisms. We have attempted to delineate the network regulatory mechanisms of fungal heat perception, regulation, response, and adaptation. Moreover, we focused on the adaption mechanism of pathogenic fungi in vivo. We also focused on to elevated temperature stress by regulating gene expression, and consequently altering their morphology and metabolites, thus contributing to fungal immune escape. These data provide support for the prevention and treatment of heat-resistant fungal infections.

Temperature sensing mechanism in fungi

Temperature perception is the first step of microbial thermal adaptation. To respond to a change in external temperature, fungal cells transmit a perception signal to an intracellular signaling system (Leach and Cowen 2014a, b). Investigations of the temperature sensing mechanism help deepen our understanding of the physiological process of thermal adaptation. At present, this thermal adaptation mechanism has been extensively studied in bacteria. RNA thermometers are the most important temperature sensing mechanism in bacteria, which can sense temperature changes without the aid of auxiliary factors (Chowdhury et al. 2006). RNA thermometers are complex RNA structures. Their conformation changes with temperature and the RNA structure can block RNA binding sites in mRNAs of key regulatory factors. Most RNA thermometers are located in the 5′-untranslated region and shield ribosome binding sites by base pairing at low temperatures. When external temperatures are elevated, the melting of RNA structures allows ribosomes to enter and initiate translation (Narberhaus et al. 2006). In plants, heat sensors recognize specific changes and activate protective mechanisms. Phytochrome and calcium signaling play a key role in sensing sudden changes in temperature and activating signaling cascades (Nishad and Nandi 2021). The theory of fungal temperature sensing was proposed a long time ago. The possibility of folding protein reactions, membrane fluidity changes, and RNA thermometers as fungal heat sensors has also been explored (Jones 2016). However, at present, investigation of fungal dissecting mechanisms is still limited. Although thermometers in fungi have been hypothesized, no relationship was found between these hypothesized thermometers and the thermal protection response of fungi (Wan et al. 2012). There are few studies on the role of fungal RNA thermometers in their own temperature sensing mechanism. Moreover, the role of RNA thermometer in fungal temperature perception mechanisms remains to be determined. However, in recent years, investigations have explored the changes in fungal structures and their signaling molecules in response to temperature fluctuations (Leach and Cowen 2014b). Whether these altered structures and their signaling molecules play roles in temperature sensing will require further investigation in fungi.

A possible link between membrane fluidity and heat shock response has been found in *Synechocystis*. Changes in the physical ordering of the *Synechocystis* membrane affect the activation of heat shock genes (Klinkert and Narberhaus 2009; Mikami and Murata 2003). Furthermore, as one of the earliest structures of fungi detected in thermal changes, the fungal plasma membrane is the most likely to act as a thermal sensor (Digel 2011). The cell membrane consists of a lipid bilayer consisting of proteins that cross the bilayer and interact with lipids on both sides of the lobules. Recent advances in lipid analysis of eukaryotic cell membranes show that they contain hundreds of various lipids (Simons and Sampaio 2011). Sphingolipids (SLs), including ceramides, sphingosine, and sphingosine-1-phosphate, are a common class of lipids in eukaryotic cells. In addition to playing a role in the cell membrane, these lipid components also act as bioactive signal molecules to regulate fungal apoptosis and senescence, cell movement, differentiation, growth, and other important life processes (Iessi et al.

2020). SLs can also dynamically aggregate with sterols to form lipid rafts or lipid rows, which serve as effective signaling and protein classification hubs (Bartke and Hannun 2009). Following heat shock of *S. cerevisiae*, the expression of enzymes in the sphingolipid synthesis pathway is upregulated. Ultimately, these molecules influence multiple biotic processes, such as actin cytoskeletal polarization, programmed cell death, and trehalose production (Chen et al. 2013; Futerman and Schuldiner 2010). These results further support the idea that SLs can act as a temperature sensor. Moreover, in the heat shock response of fungi, SLs link necessary metabolic processes to a range of different cellular functions required for temperature and pressure responses (Jenkins et al. 1997). In addition to SLs, many lipids also serve as signaling molecules (e.g., ceramide (Cer) and long chain bases) in response to temperature stimuli, thus playing a regulatory role in the temperature stress response (Shapiro and Cowen 2012). For example, high temperature stress can also induce the expression of Cer and its derivatives (Wells et al. 1998). Lysophospholipids are also subjected to temperature stress and respond to signals to assist in the cell thermal adaptation process (Fabri et al. 2020). To respond to temperature stress, lipid molecules in the plasma membrane and SL composition and enzyme activity in the SL pathway change, triggering intracellular signals to respond to temperature and pressure and acting as part of fungal temperature sensing.

Stress-induced acidification is widespread in eukaryotes, including mammals, insects, plants, and fungi (Kroschwald et al. 2015; Triandafillou et al. 2020). Heat shock induces transient intracellular acidification, an intracellular change that enhances stress resistance in eukaryotes (Tombaugh and Sapolsky 1993). It was previously thought that HSF1 activation was triggered only by heat-induced misfolded proteins in *S. cerevisiae* (Baler et al. 1992). However, a recent study confirmed that HSF1 can be strongly activated during cytoplasmic acidification when protein synthesis is inhibited. This acidification process is necessary to induce a heat shock response in the translation of suppressed cells. Heat-triggered acidification also increases population fitness and promotes cell cycle re-entry upon heat shock (Triandafillou et al. 2020). This finding suggests another pathway for HSF1 activation. In addition to the association between intracellular misfolded proteins and HSF1 activation, something may trigger cytoplasmic acidification; HSF1 activation may play a role in cell temperature perception. To date, studies on intracytoplasmic acidification caused by heat stress have been performed only in *S. cerevisiae* and remain to be explored in pathogenic fungi. Strengthening research on this topic may provide a new direction to explore the heat resistance mechanisms of pathogenic fungi.

Recent studies have revealed that *Arabidopsis thaliana* phytochrome B, a red light receptor, binds target genes in a temperature-dependent manner and participates in its own temperature sensing mechanism (Jung et al. 2016; Rockwell and Lagarias 2017). Interestingly, the same phenomenon has been found in the filamentous fungus *Aspergillus nidulans*. The heterohistamine kinase TcsB and photochrome FphA participate in their own temperature sensing. Moreover, the temperature-activated photochrome provides input signals into the high-osmolarity glycerol (HOG) signaling pathway (Yu et al. 2019). However, to date, investigation of the fungal temperature sensing mechanism network has been limited. When discussing the temperature sensing mechanism of fungi, there are many questions worth exploring. Fungi are subjected to different degrees of temperature stress during infection and to fluctuating temperatures in nature. For both environmental and pathogenic fungi, mechanisms to quickly sense changing temperatures are highly important for adaptation to new temperature stress. However, few studies have examined the mechanisms of the temperature sensor network, and further research is needed to reveal these specific mechanisms. In addition, when studying the temperature sensing mechanism in fungi, we need to distinguish whether the response is a signal from the cell's perception of ambient temperature, or a thermal adaptation after perception of ambient temperature.

Conserved genes and transcription factors in fungi play an important regulatory role in heat adaptation

HSF1 and heat shock proteins

After the fungal temperature sensor transmits the signal into the cell, transcription factors related to heat adaptation regulate gene expression, improving fungal survival at the increased temperature. HSFs are important regulators for heat stress survival in eukaryotes. There are four different HSF members in mammals and plants: HSF1–HSF4. Yeast expresses only a single HSF that performs a similar function to HSF1 (Akerfelt et al. 2010). In fact, HSF1 does not act as a master regulator of the thermal shock response, but rather controls the expression of a set of genes that induce the expression of molecular chaperones and other target proteins that restore protein folding homeostasis. These protein chaperones are called heat shock proteins (HSPs) (Pincus 2017). HSF1 exists as an inactive monomer or dimer in eukaryotes and hides acidic groups in the cytoplasm. Under heat stress, HSF1 forms a homologous trimer that binds to heat shock elements (HSEs) of the nGAAn sequence repeat unit, thus upregulating the expression of HSPs. However, in *S. cerevisiae*, HSF1 binds HSEs as a trimer at normal temperature, and phosphorylation and other posttranslational modifications directly stimulate HSF1 activity and regulate

transcription of HSPs after heat shock (Gao et al. 2016). An evolutionarily conserved HSF1 is also expressed in *Candida albicans*. This transcription factor participates in the global transcriptional response to heat shock by inducing transcription through HSEs, which is essential for *C. albicans* survival. Interestingly, Hsf1 proteins of *C. albicans* and *S. cerevisiae* have different binding affinities. Analysis of the motif binding HSF1 has revealed a common sequence between human and *S. cerevisiae*, comprising three reverse nGAAn repeat patterns. *C. albicans* Hsf1 binds nGAAn elements in at least three configurations in different dimeric and trimeric forms. The TTCnnGAAnnTTC element has the strongest binding ability, whereas GAAnnTTC and TTCn7TTC have lower but still significant binding affinity (Leach et al. 2016; Nair et al. 2018). HSF1 of *C. albicans* is rapidly phosphorylated after heat shock at 30–42 °C followed by dephosphorylation. However, the molecular memory for this reaction is short, fading within 2 h (Leach et al. 2012b). In addition, following acute heat shock of *C. albicans*, HSF1 binds distinct motifs in nucleosome-depleted promoter regions to regulate heat shock genes and genes associated with virulence. Under heat shock conditions, *C. albicans* responds to temperature through HSF1 and Hsp90 coordinating gene expression and chromatin structure, resulting in heat adaptation and changes in virulence (Leach et al. 2016). The main function of HSF1 in *Aspergillus fumigatus* is to regulate the HS response and regulate the expression of heat shock proteins. HSF1 also enhances the heat resistance of *A. fumigatus* by regulating cell wall biosynthesis and remodeling and expression of genes related to lipid homeostasis (Fabri et al. 2021). The discovery of homologues of HSF in different fungi also confirms the high conserved nature of this ancient response process in organisms.

Hsp70 is a proximal sensor of HSF1-mediated cell protection that can distinguish between two different environmental stressors (Wang et al. 2012). In the heat shock response, misfolded cytoplasmic proteins titrate Hsp70 to activate HSF1 in the nucleus (Masser et al. 2019). There are two interaction sites between Hsp70 and HSF1 in *S. cerevisiae*. Elimination of Hsp70 regulation of HSF1 results in overall dysregulation of HSF1 transcriptional activity. When both loci are destroyed simultaneously, there is a synergistic effect on gene expression and cellular fitness (Peffer et al. 2019). Hsp70 and Hsp90 are the main HSPs regulated by HSF1. These two protein chaperones form a negative feedback loop with HSF1. The regulatory roles of HSP70 and HSF1 have been demonstrated. However, the interaction between HSP90 and HSF1 requires further evidence. This regulatory circuit can coordinate the heat shock response of the cell with its external environment (Krakowiak et al. 2018; Masser et al. 2020). Heat shock protein Hsp104 in yeast, a homolog of bacterial ClpB, works with the Hsp70 chaperone system to reactivate denatured proteins (Miot et al. 2011). FpHsp104, a homolog of yeast Hsp104 in the plant pathogen *Fusarium pseudograminearum*, plays an important role in heat tolerance development and pathogenicity (Xia et al. 2021). There is a new type of Hsp104 regulation called delayed upregulation (DUR). DUR is regulated by HSEs and involves Msn2/4P-regulated gene products (Seppa et al. 2004). Moreover, *Ssd1*, an essential gene for Hsp104-mediated protein disaggregation, regulates cell heat resistance and cell wall remodeling; it also affects the ability of Hsp104 to bind protein aggregates (Mir et al. 2009). Overexpression of Hsp25 in *Metarhizium robertsii* promoted fungal growth under heat stress and enhanced the tolerance of heat shock-treated spores to osmotic stress (Liao et al. 2014). SHSPs are found in a variety of fungi, including *Aspergillus*, *Magnaporthe*, *Fusarium*, and *Penicillium* (Wu et al. 2016).

Mitogen-activated protein kinase (MAPK) Hog1 and its related transcription factors and interacting proteins

Hog1, the central MAPK of the HOG signaling pathway, is activated in response to fluctuations in environmental osmotic stress. Initially thought to be activated only by osmotic stress, it was later shown that Hog1 can also be activated by heat stress and play an important role in resisting heat stress (Fig. 1) (Dunayevich et al. 2018). Moreover, Hog1 stimulated by heat stress depends on the cell wall integrity (CWI) signaling pathway and membrane-bound osmosensor Sho1 (Dunayevich et al. 2018). Activated Hog1 helps promote recovery of cell damage caused by heat stress (Winkler et al. 2002). Recently, a chemical genetics approach demonstrated that the bulk of the heat shock response is independent on HSF1. Most genes induced by heat stress are controlled by Msn2 and Msn4, C2H2-type zinc-finger proteins downstream of Hog1 (Pincus 2017). Msn2 and Msn4, as stress-induced transcription factors that regulate general stress responses, can be activated by a variety of stress responses, including carbon source hunger, heat shock, and severe osmotic and oxidative stress. Therefore, they can regulate most heat-resistant genes (Johnson et al. 2021; Stewart-Ornstein et al. 2013). For example, they regulate expression of the *Nth1* gene, which encodes neutral trehalase in *S. cerevisiae*, thus regulating the hydrolysis of trehalose under different stress conditions. They also maintain trehalose concentration under stress by regulating trehalose synthesis and hydrolase expression (Zahringer et al. 2000). Msn2 may also help to cope with high temperatures by regulating genes related to lipid metabolism, which in turn alters membrane fluidity (Li et al. 2017). Interestingly, there are different roles of HSF1, Msn2, and Msn4 in ensuring cell survival and growth before and after a fungus is exposed to extreme temperatures. HSF1 activates transcription of most of its target genes during the recovery period after severe

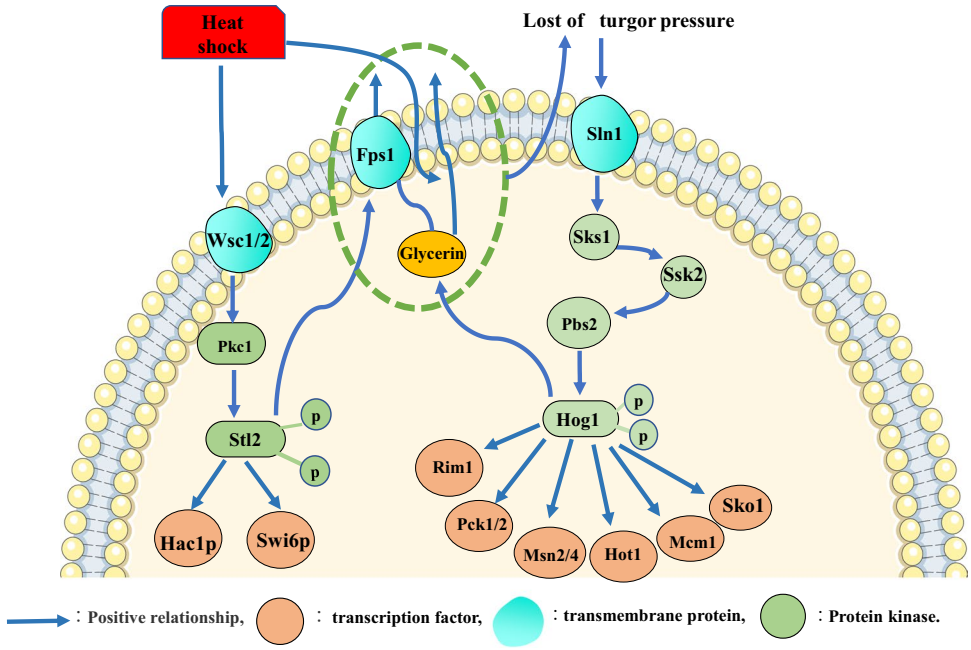

Fig. 1 Regulatory mechanism of high-osmolarity glycerol (HOG) and the cell wall integrity (CWI) pathway under heat stress. Heat shock stimulates intracellular glycerol outflow through the HOG pathway and CWI pathway, thus decreasing expansion pressure

heat shock. Delayed upregulation of HSF1 is induced by accumulation of misfolded proteins in heat-shocked cells, which are necessary to restore normal cell growth. By contrast, Msn2 and Msn4 are not involved in delayed gene upregulation; they function prior to high temperature exposure. However, they are also indispensable for cell growth during recovery (Yamamoto et al. 2008). Similar transcription factors, CaMsn4 and CaMsn2, have been identified in *C. albicans*, although they were not found to play a significant role in the stress response (Nicholls et al. 2004).

OLE1, a gene encoding the delta-9 fatty acid desaturase in *S. cerevisiae*, catalyzes the production of monounsaturated fatty acids from saturated fatty acids (Lutz et al. 2019). *OLE1* plays an important role in tolerance to multiple stresses (Covino et al. 2016). The content of oleic acid in the membrane was significantly increased and the strain surface was more tolerant to various stresses in ectopic overexpression of *OLE1*. Interestingly, after deletion of Hog1, the *OLE1*-mediated tolerance to multiple stresses significantly decreased. Further investigation confirmed that Hog1 had a positive regulatory effect on *OLE1*-mediated multiple stress tolerance (Nasution et al. 2017). Moreover, *OLE1* overexpression constitutively activates Hog1 through Ssk2. Spt23 and Mga2, two highly conserved membrane-bound transcriptional regulators in fungi, regulate a large number of expressed genes involved in ribosomal biogenesis and lipid metabolism. *OLE1* is the major target gene regulated by Mga2 and Spt23 (Covino et al. 2016). The ratio of saturated to unsaturated acyl chains in the membrane lipid is a key factor determining the fluidity and phase behavior of the membrane. *S. cerevisiae* maintains membrane fluidity through *OLE1*-activated unsaturated fatty acids as lipid building blocks. Membrane fluidity is increased by increasing unsaturated fatty acid content and/or decreasing average fatty acid length or sterol content. This regulation enhances plasma membrane stability (Ballweg and Ernst 2017). *OLE1* overexpression in *S. cerevisiae* at high temperature also contributes to a reduction in lipid peroxidation induced by heat stress. In this way, oxidative damage of the plasma membrane can be reduced and the heat resistance of cells can be enhanced (Li et al. 2019).

Other signaling pathway and transcription factors

The cAMP (CAMP)/protein kinase A (PKA) signaling pathway is one of the most important eukaryotic signaling pathways. This pathway is central in the transduction of fungal environmental signals, and the mediation of various cellular functions and heat tolerance in many fungi. The TPK1 subunit of *S. cerevisiae* PKA is involved in chromatin remodeling under heat stress, thus enabling adaptation to changing environments (Reca et al. 2020) . Compared with wild type *A. flavus*, the *ΔacyA-C* (adenylate cyclase gene) strain shows significantly lower heat tolerance (Yang et al. 2016b). Studies on *ΔPka* mutants of *C. albicans* have indicated that this pathway plays an important role in resistance to heat, and oxidative and salt stress (Giacometti et al. 2009a). Moreover, this signaling pathway is important for heat resistance in *C. auris* (Kim et al. 2021).

The calcium-calcineurin signaling pathway is highly conserved and plays an important role in fungal adaptation to host or environment stress, expression of virulence factors, and growth and development (Juvvadi et al. 2017). The calcineurin responsive zinc finger transcription factor Crz1

plays an important role in heat resistance in *B. bassiana* (Li et al. 2015). Importantly, calcineurin and its downstream target Crz1 have also been shown to regulate heat tolerance and virulence expression in *C. glabra* (Chen et al. 2012). Transcriptome analysis has indicated that Crz1 in *C. neoformans* regulates genes that aid in resistance to heat damage during heat stress (Chow et al. 2017). However, no phenotype associated with temperature sensitivity has been found in *C. albicans crz1Δ* mutants (Delarze et al. 2020). In *C. albicans*, TPK1 and TPK2, two catalytic subunits encoding PKA, play roles in response to heat and oxidative stress (Giacometti et al. 2009). No temperature-related phenotypic change has been observed in the *Aspergillus flavus crz1Δ* mutant (Lim et al. 2019).

In addition to those described above, other transcription factors involved in cross-tolerance that play a role in fungal resistance to heat stress were found. In *S. cerevisiae*, the *LRE1* gene acts independently of the CAMP and PKA pathways. However, the homologous genes have not been studied in other pathogenic fungi. Lre1 plays a role in resisting heat stress by inhibiting the protein kinase Cbk1 in *S. cerevisiae*. Overexpression of this transcription factor can affect the expression of chitinase and trehalose accumulation (Versele and Thevelein 2001). Swi6p and Hac1p, cell division transcription factors, are involved in the unfolded protein response and play an important role in the maintenance of *S. cerevisiae* heat shock resistance (Jarolim et al. 2013). Swi6p and Hac1p homologues are present in *C. albicans* but do not play roles in heat resistance. The homologues regulate the proliferation of *C. albicans* and their hyphal growth (Hussein et al. 2011). BbThm1, a member of the Zn(II) 2CYS6 (Gal4-like) family in *Beauveria bassiana*, had been shown to enhance cell resistance to heat stress and play an important role in other stresses, including oxidative osmosis and various fungicides (Huang et al. 2019b). Compared with other factors that regulate the tolerance response of multiple fungi to heat stress, these factors that exist only in single fungi might have conferred unique advantages in the process of epigenetic evolution.

The role of fungal enzymes and other metabolites in heat adaptation

Fungal transcription factors regulate gene expression to encode enzymes and other metabolites during heat adaptation; these products are summarized in Table 1. This class of substances can be used to protect cells from damage caused by rising temperatures. Oxidative damage is one of the major secondary effects of heat shock. When cells are exposed to higher temperatures, the oxygen respiration rate increases and ROS accumulate in the cells, resulting in increased intracellular oxidation and cell damage (Moraitis and Curran 2004). Fungi secrete a variety of antioxidant enzymes in response to oxidative stress. Superoxide dismutase plays a protective role in the body by converting superoxide radical to hydrogen peroxide (Ribeiro et al. 2017). Interestingly, in addition to their antioxidant function, peroxide-reduced proteins can also act as molecular chaperones and signal transduction regulators (Gao et al. 2016; Ribeiro et al. 2017; Wood et al. 2003). Pyruvate in the spores of *M. robertsii* was found to accumulate rapidly under heat stress; this occurs earlier than the above enzymes and is the first reactive oxygen scavenger after heat treatment. Heat stress can also induce pyruvate accumulation in other fungi, including *A. fumigatus*, *Cordyceps militaris*, *Magnaporthe oryzae*, *Neurospora crassa*, and *S. cerevisiae* (Zhang et al. 2018). By secreting pyruvate, fungi can effectively reduce protein carbonylation, stabilize mitochondrial membrane potential, and promote fungal growth (Zhang et al. 2017).

Glutathione, a common antioxidant, is synthesized under the catalysis of γ-glutamyl cysteine synthase (*Gsh1* gene) and glutathione synthase (*Gsh2* gene). During heat shock stress, *S. cerevisiae* induces the expression of *Gsh1* and *Gsh2* in a YAP1-dependent manner, which is followed by increased intracellular glutathione content (Sugiyama et al. 2000a). Further study has demonstrated that heat shock-induced glutathione synthesis protects mitochondrial DNA from oxidative damage (Sugiyama et al. 2000b). Most studies have focused on the role of endocrine glutathione in fungi. A recent study showed that *S. cerevisiae* and their offspring can survive and replicate at high temperatures by helping each other. Further investigation found that glutathione, secreted by yeast, accumulates in large quantities outside the cell, which could eliminate harmful extracellular chemicals and prevent yeast from dying at high temperatures (Laman Trip and Youk 2020). The monothiol glutaredoxins Grx3 and Grx4 are important regulators of iron homeostasis in *S. cerevisiae*. They generally play an important role in (2Fe-2S) cluster sensing and transport (Martinez-Pastor et al. 2017). Moreover, Grx3 and Grx4 also play an additional role in the resistance of *S. cerevisiae* to oxidative stress (Mechoud et al. 2020). In addition, the loss of *Grx4* would decrease the heat resistance and damage cell wall integrity in *C. neoformans*. At the same time, Grx4 and calcineurin signaling jointly affect the heat tolerance of *C. neoformans* (Hu et al. 2021).

Some studies have classified a variety of fungi, including Eurotiales, Mucorales, and Onygenales. These fungi can be classified as heat-resistant, thermophilic, and mesophilic. The peptidase of thermophilic fungi and mesophilic fungi has been compared and analyzed. The peptidase of thermophilic fungi can adapt to high temperatures. The amino acid sequence of the peptidase protein was found to be significantly different. Compared with mesophilic fungi, the proportion of hydrophobic and charged amino acids in

Table 1 Summary of proteins and metabolites associated with fungal heat adaptation

Proteins or metabolites	Fungal species	The role in respond to heat stress	Corresponding references
Lre1	*Saccharomyces cerevisiae*	It increased trehalose accumulation and heat resistance and regulated the expression of the cyclin genes	Versele and Thevelein (2001)
Swi6p/Hac1p	*S. cerevisiae*	They shared contributions to the regulation of temperature, cell wall, and other stresses response	Jarolim et al. (2013)
Grx3/Grx4	*Cryptococcus neoformans*	Grx4 is required for membrane and cell wall integrity	Hu et al. (2021)
BbThm1	*Beauveria bassiana*	Used as transcription factor for heat and membrane integrity	Huang et al. (2019b)
CgSTE11	*Candida glabrata*	It mediates crosstalks between MAPK signaling pathways in response to environmental challenges	Huang et al. (2019a)
SSD1	*S. cerevisiae*	Gene is necessary for Hsp104-mediated protein breakdown	Mir et al. (2009)
Superoxide dismutase	Most fungi	It converts the superoxide anion into hydrogen peroxide and responds to oxidative stress	Ribeiro et al. (2017)
Catalase	Most fungi	Used as antioxidants or molecular chaperones to regulators of signal transduction	Gao et al. (2016)
Peroxiredoxin	Most fungi	It acts as molecular chaperones and signal transduction regulators	Wood et al. (2003)
Ct1	*C. neoformans*	Cts1 is a substrate of calcineurin during high-temperature stress responses	Aboobakar et al. (2011)
Cyr1 and PKA	*Candida auris* *Aspergillus flavus* *Candida albicans*	They play an important role in promoting *C. auris* growth and enhancing heat stress and antifungal drugs resistance	Giacometti et al. (2009); Kim et al. (2021); Yang et al. (2016a)
Pyruvate	*Aspergillus fumigatus*, *Cordyceps militaris*, *Metarhizium robertsii*, *Magnaporthe oryzae*, *Neurospora crassa*, *S. cerevisiae*	By secreting pyruvate, fungi can effectively reduce protein carbonylation, stabilize mitochondrial membrane potential, and promote fungal growth	Zhang et al. (2017)
Glutathione	Most fungi	It protects mitochondrial DNA from oxidative damage	Sugiyama et al. (2000a); Sugiyama et al. (2000b)
Trehalose	Most fungi	Used as a protein stabilizer and promotes survival in extreme heat conditions	Luo et al. (2021); Piper (1993)
Glycerin	*S. cerevisiae*	Maintain yeast osmotic pressure balance and the stability	Li et al. (2009)
Arabitol	*Penicillium roqueforti* *Rhizomucor miehei*	Arabitol may form the core of heat resistance of *P. roqueforti* conidia	Ianutsevich et al. (2020); Punt et al. (2020)

thermophilic fungi peptidase was increased while the proportion of polar amino acids was decreased (de Oliveira et al. 2018). Interestingly, 400 proteins (200 thermophiles and 200 mesophiles) in multiple databases have been studied to assess their amino acid preferences. A high frequency of hydrophobic salt bridges and smaller volume non-polar residues (Gly, Ala, and Val) in thermophilic proteins has been observed. However, the frequency of larger polar residues was low in thermophiles. This phenomenon may be caused by the preference of thermophilic proteins to small non-polar amino acids and the change in residual physical and chemical properties and an increase in salt bridges (Panja et al. 2015). This result is consistent with the observation of thermophilic and mesophilic fungi in previous studies (de Oliveira et al. 2018). Further studies are needed to investigate the differences in heat resistance of phylogenetically related species and the differences in peptidase structure.

In addition, as a substance secreted by fungi to aid in heat adaptation, trehalose was discovered more than two decades ago. Many investigations have confirmed that trehalose plays an important role in the early heat shock response (Luo et al. 2021). In addition to *S. cerevisiae*, trehalose has been

shown to play a protective role in heat stress in *C. albicans* (Arguelles 1997), *C. neoformans* (Ngamskulrungroj et al. 2009), and *C. parapsilosis* (Sanchez-Fresneda et al. 2014). Trehalose enables proteins to maintain their conformation at high temperatures and inhibits the aggregation of denatured proteins. It also helps the fungus to survive in extreme heat conditions (Arguelles 1997; Piper 1993). However, failure to degrade trehalose after the heat shock response may impair cell recovery from heat shock (Singer and Lindquist 1998). A recent study showed that increased intracellular trehalose levels following heat stress led to increased osmotic pressure in *Schizosaccharomyces pombe*, which in turn activates the cell wall integrity pathway. In the fungal heat shock response, there is a synergy between trehalose, heat shock proteins, and lipids to maintain cell membrane integrity (Peter et al. 2021). Glycerol is also synthesized during the sensitive response period of heat shock. It can maintain osmotic pressure balance and enzyme stability in yeast during heat shock. It also prevents the enzyme from being inactivated at high temperature (Blomberg 2000; Li et al. 2009; Zancan and Sola-Penna 2005). Arabitols, secreted by *Penicillium roqueforti*, have also been shown to play an important role in heat resistance (Punt et al. 2020). Arabinol has been shown to help resist osmotic stress in the salt-tolerant fungus *Fusarium* sp. (Smolianiuk et al. 2013). Further investigation has shown that arabinol is highly expressed in the thermophilic fungus *Rhizomucor miehei*, thus suggesting that this product may help fungi resist osmotic stress under heat stress (Ianutsevich et al. 2020). Interestingly, *C. albicans* has been found to resist oxidative and osmotic stress by accumulating glycerol and arabitol in the cell (Sanchez-Fresneda et al. 2013). Additionally, *A. fumigatus* can decrease the damage caused by osmotic stress by accumulating glycerol (Schruefer et al. 2021). Whether glycerol and arabinol secreted by these pathogenic fungi may help them survive under high temperature stress requires further investigation.

Morphological and structural changes of fungi under heat stress

In the face of temperature stress, fungi change morphology and structure by perceiving ambient changes in temperature. Many studies have focused on this in recent years. Observation of the morphology and microstructure of cells following heat treatment are summarized in Fig. 2. The classic morphogenesis is thermophilic diphasic fungi, which includes *Coccospora* and *Histoplasma capsulatum*. These fungi can change form at high temperatures, enhancing their virulence (Klein and Tebbets 2007). In nature, *H. capsulatum* grows in the soil as mold and forms spore-producing hyphae. After

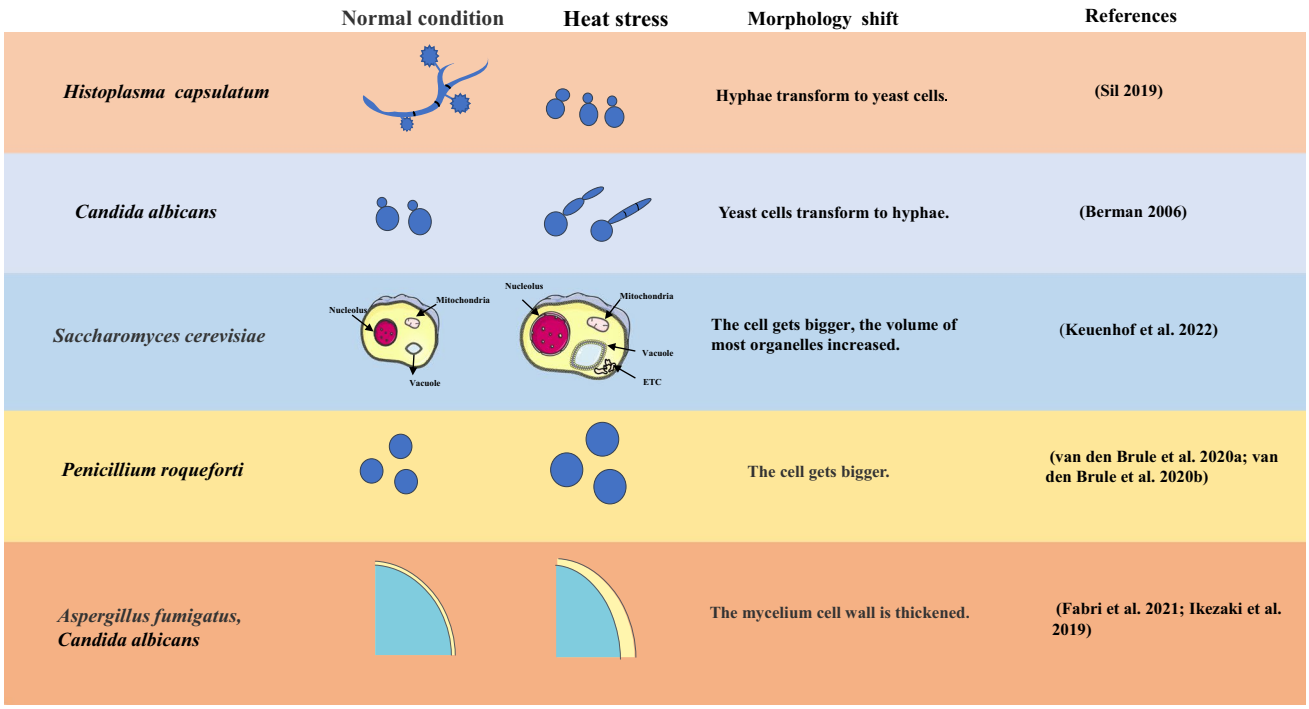

Fig. 2 The observing morphology and microstructure change of cells after heat shock. Under external heat stress, some fungi transition between the yeast and mycelium states. Simultaneously, the spore volume of some fungi increases, the organelles inside the spore also markedly change, and unknown structures (electron-translucent structure) even appear

these spores are inhaled into the mammalian host, the host body temperature causes the mycelium to change to a yeast shape and induce expression of virulence-related genes (Sil 2019). The mechanism underlying the temperature response in *H. capsulatum* has been elucidated. Ryp4, a transcription factor, was identified by analyzing the Ryp regulatory circuit. Ryp4 was found to be necessary for growth and gene expression at the yeast stage and is regulated with Ryp1, Ryp2, and Ryp3. This pathway regulates the transition of *H. capsulatum* between yeast and filamentous forms in response to temperature changes (Beyhan et al. 2013). By contrast, *C. albicans* grows yeast-like at ambient temperature while a morphological filamentous form was induced at high temperature (Berman 2006). This transformation of *C. albicans* to different forms requires the formation of actin lines to coordinate the growth of polarized cells. The triprotein complex BNi1-BUD6-AIP5 coordinates nucleation in actin cable assembly and hyphal growth, thus assisting in filamentous transformation (Xie et al. 2020). Moreover, at room temperature, overexpression of *C. albicans* HSF1 results in upregulation of positive regulators of filamentation (including Brg1 and Ume6), which control the filamentous morphology of *C. albicans* (Veri et al. 2018). Thus, filamentous transformation may be conserved in various filamentous fungi and yeasts.

Paracoccidioides brasiliensis is a pathogenic fungus causing paracoccidioidomycosis. After changing culture conditions, such as temperature or carbon dioxide, the fungus is induced to transition from mycelia to pathogenic yeast. Transcriptional analysis of the mycelium and yeast forms of *P. brasiliensis* has revealed upregulation of a variety of genes in yeast cells responding to heat shock and involved in defending against oxidative stress, including *HSP90*, *HSP70*, *HSP60*, and other genes encoding heat shock proteins and oxidoreductases (Felipe et al. 2005). Another transcriptome analysis has found that the most upregulated genes encode exomeric proteins expressed only on the surfaces of yeast cells. In addition, a variety of genes related to virulence and stress response are upregulated (Carlin et al. 2021). In fact, the morphological changes in thermo-dimorphic fungi are largely caused by temperature stimulation. Meanwhile, the upregulation of transcription factors related to the stress response after morphological change also indicates that the morphological transformation may facilitate better survival during the heat adaptation process. However, whether the transformation of fungal morphology directly increases tolerance to high temperatures, or is an unrelated phenotype caused by stress during fungal heat adaptation, remains to be studied.

Recent studies have begun to focus on the structural changes of fungi under heat stress, confirming that the morphological changes of fungal spores themselves are also correlated with heat resistance. For example, cells were found to be larger following heat shock treatment than in an untreated group in *S. cerevisiae* (Keuenhof et al. 2022). The conidial size of *P. roqueforti* formed at 30 ℃ was also 12–14% larger on average than that at 15 ℃ and 25 ℃ (Punt et al. 2020). The average spore size of *Paecilomyces variotii* was also positively correlated with heat resistance. In addition, spore ratio roundness was also significantly correlated with heat resistance. Elliptic spores of heat-resistant strains were more spherical than those of heat-sensitive strains, while those of sensitive strains were more elongated in *P. variotii* (van den Brule et al. 2020a; van den Brule et al. 2020b). In recent studies on osmotic stress of *S. cerevisiae*, significant changes in volume spores were also observed. Further analysis showed that the change in cell volume was related to yeast metabolism under osmotic stress (Saldana et al. 2021). Osmotic stress affects both growth control and the cell cycle, resulting in abnormal fungal spore morphology. This unusual morphology results from crosstalk between upstream components of the HOG pathway (Brewster and Gustin 2014). Fungi not only undergo osmotic stress, but also have a direct influence of thermal shock during heat treatment. It is unclear whether the change in cell volume is related to metabolic enhancement under stress. Moreover, the mechanisms underlying spore enlargement and structural changes in some organelles following heat treatment have not been elucidated.

The internal microstructure of fungal spores also changes dramatically under heat stress. The organelle structure of *S. cerevisiae* was significantly altered by mild and continuous heat shock at 38 ℃ (Keuenhof et al. 2022); the volumes of most organelles, including vacuoles, mitochondria, nuclei, and multivesicular bodies (MVBs), were increased while the volume of cytoplasm decreased. MVB volume was increased nearly 70%. Notably, the authors also observed electron-translucent structure aggregates near the cell membrane; this process may be related to increased membrane fluidity (Keuenhof et al. 2022). MVBs are involved in the transport of ubiquitin compounds in cells, which may be related to the increased intracellular degradation (Henne et al. 2011). Changes in MVB structure may accelerate the degradation of folded proteins that have accumulated in cells due to the heat shock response. However, the mechanism of the above-mentioned changes in organelles after heat treatment has not yet been explored. ZCF8, a previously unidentified transcription factor in *C. albicans*, maintains vacuolar homeostasis when fungi are exposed to fluctuations in nitrogen. Overexpression of ZCF8 increased the number of large vacuoles in *S. cerevisiae* (Reuter-Weissenberger et al. 2021). Fungal vacuole enlargement was observed under both heat stress and nitrogen stress. This suggests ZCF8 may also be involved in the regulation of vacuolar morphology changes under heat stress. In addition to the changes in internal microstructure, it was also found that after 5 min of heat shock, the cell wall

became significantly thicker in *A. fumigatus*. Further investigation found that short-term heat shock stress simultaneously triggered co-expression of HSF1 and HSP90. PkcA and MpkA of the CWI signaling pathway also regulate HSF1 and Hsp90 expression. Each pathway component interacts with the cell wall to enhance heat resistance in *A. fumigatus* (Fabri et al. 2021). However, the mechanism underlying HSF1-mediated thickening of the *A. fumigatus* cell wall has not yet been elucidated. The mycelium of *C. albicans* also thickens after heat shock treatment (Ikezaki et al. 2019). Hsp90 also regulates activation of Mkc1, Hog1, and Cek kinases during heat shock in *C. albicans*. This regulation can affect cell wall structure for a long time and lead to heat resistance of *C. albicans* (Leach et al. 2012a). These results suggest a need to explore the mechanism of organelle morphological changes during fungal heat adaptation by studying the regulatory circuits composed of multiple signaling pathways and transcription factors associated with the fungal stress response.

Thermal adaptation of pathogenic fungi in vivo

In addition to thermal shock in the natural environment, pathogenic fungi are also affected by thermal shock in mammalian hosts. The fungus spreads from the environment to various host sites, including the mouth, lungs, blood, and central nervous system. In response to pathogenic fungal infection, the host produces both exogenous and endogenous pyrogens through a series of signals that travel to the brain. These pyrogens activate heat neurons in the anterior hypothalamus to achieve a higher thermal balance point, resulting in fever (Ogoina 2011). This increased temperature leads to heat stress for the invading pathogens. At the same time, the body's immune system quickly responds to the invading pathogens. The detection and elimination of fungal pathogens depends on phagocytes of the innate immune system, especially macrophages and neutrophils (Erwig and Gow 2016). Invading fungi respond to the elevated temperature stress by regulating gene expression to alter their morphology and metabolites, which contribute to fungal immune escape (Hopke et al. 2018).

Melanin is a dark green, brown, or black antioxidant polyphenol pigment required for the secretion of many fungal pathogens to maintain pathogenicity (Lee et al. 2019). Melanin production significantly enhances the virulence of human pathogenic fungi and contributes to the survival of fungi in harsh environments (Nosanchuk et al. 2015). *A. fumigatus* produces at least two types of melanin, pyomelanin and dihydroxynaphthalene (DHN) melanin. Pyomelanin protects fungi from ROS and acts as a defensive compound in response to cell wall stress (Keller et al. 2011; Schmaler-Ripcke et al. 2009). Pksp is a precursor in the formation of DHN-melanin. Active PksP not only inhibits apoptosis of phagocytes by interfering with host PI3K/Akt signaling, but also effectively inhibits the acidification of conidium-containing phagosomes. These features enable *A. fumigatus* to survive in phagocytes and to escape human immune effector cells, successfully multiplying in humans (Couger et al. 2018; Heinekamp et al. 2012). *C. neoformans* is a fungus that has been well studied in vivo. Its polysaccharide capsules and melanin aid in immune system escape (Matsumoto et al. 2019). It has been shown that melanin production, regulated by CAMP and the HOG pathway, improves *C. neoformans* resistance to heat and ROS, which help the fungi survive at human temperatures (Kwon-Chung and Rhodes 1986). A recent investigation showed that melanin synthesis is also associated with the regulation of HSF1. Four direct targets of HSF1 have been found in the plant pathogen *Colletotrichum gloeosporioides*, all of which are the melanin synthesis gene *CgHSF1*, which activates melanin biosynthesis through transcription (Gao et al. 2022). In addition to the secretion virulence factor, adaptation of *C. neoformans* to host core temperature is accompanied by a decay of ribosomal protein mRNA mediated by CCR4, the major mRNA deadenylase. RNA decay also regulates exposure of *C. neoformans* cell wall glucan to avoid phagocytosis by immune cells (Bloom et al. 2019).

Amino acid transport is an important nutritional mechanism for fungi. A variety of amino acid permeases of *C. neoformans* can help resist environmental stress. These amino acid permeases can function at elevated temperatures, thus allowing amino acid transport to occur at unfavorable temperatures to ensure proper nutrient supply (Martho et al. 2016). Moreover, the roles of amino acid permeases of *C. neoformans* in resisting environmental stress have been confirmed to be related to Ras signal transduction (Calvete et al. 2019). However, amino acid permease in *C. albicans* does not show a temperature-related phenotype, and the amino acid permease Gap4 induces morphogenesis of *C. albicans* by participating in S-adenosylmethionine transport (Kraidlova et al. 2016). Furthermore, many natural fungi also change drastically when they enter their mammalian hosts. This change in temperature gradient from the environment to the body triggers the fungal adaptive development program (Gow et al. 2002). Colonization of *C. albicans* in the gastrointestinal tract is enhanced by the coexistence of mycelium and yeast (Witchley et al. 2019). By sensing ambient temperature, thermal-biphasic fungi, such as *Blastomyces dermatitidis*, *H. capsulatum*, *Penicillium marneffei*, and *Sporothrix schenkii*, could undergo mycelium-to-yeast transformation (Casadevall 2017), enhancing their pathogenicity and immune evasion.

At present, because of the complex internal conditions of the body, there are few studies on fungal thermal adaptation

in human infections. To survive in a host, pathogenic fungi must survive temperature stress, nutrient stress, acid–base stress, oxidative stress, and immune response stress. It is thus difficult to study the effect of a single factor, body temperature, on invasive fungi. These multiple stresses jointly regulate the expression of genes related to the stress response through multiple signal transduction pathways. These multiple responses may help fungi enhance their adaptation to internal stress and accelerate pathogenic infection. In fact, when pathogenic fungi are exposed to a single stress signal in the body, they also increase their tolerance to other stresses (Brown et al. 2019; Mitchell et al. 2009). Human temperature is an important factor that triggers expression of virulence genes in pathogenic fungi to cope with various stresses. Therefore, further investigation of how fungi adapt to heat stress in the human body will be important.

Conclusion

In this review, we summarize the latest research on the mechanisms of heat resistance in fungi and classify them into network regulatory mechanisms of heat perception, transcriptional regulation, response, and adaptation. We also discussed the process of heat adaptation of pathogenic fungi in vivo. Pathogenic fungi can strengthen their immune escape ability when stimulated by changes in human body temperature. An outline of the fungal thermal adaptation mechanism is shown in Fig. 3. A complex signal regulation network underlies each part of the fungal heat adaptation process. Each network will require further investigation. In general, fungal heat stress is accompanied by oxidative and osmotic stress, as well as immune response stress in the body (Kwon-Chung and Rhodes 1986). There are many shared regulatory elements in the responses to these abovementioned stresses in fungi (Caspeta and Nielsen 2015). For example, CgSTE11 of *C. glabrata* plays an important role in high temperature tolerance and broad cross-tolerance to other environmental stresses, including acids, alcohol, and oxidants (Huang et al. 2019a). We previously showed that there are cross-linkages between regulatory elements, signaling pathways, and transcription factors, in the resistance to various stresses (Song et al. 2016; Xin et al. 2020). These provide clues that elements of other stress response pathways may play an identical or similar role in fungal heat tolerance

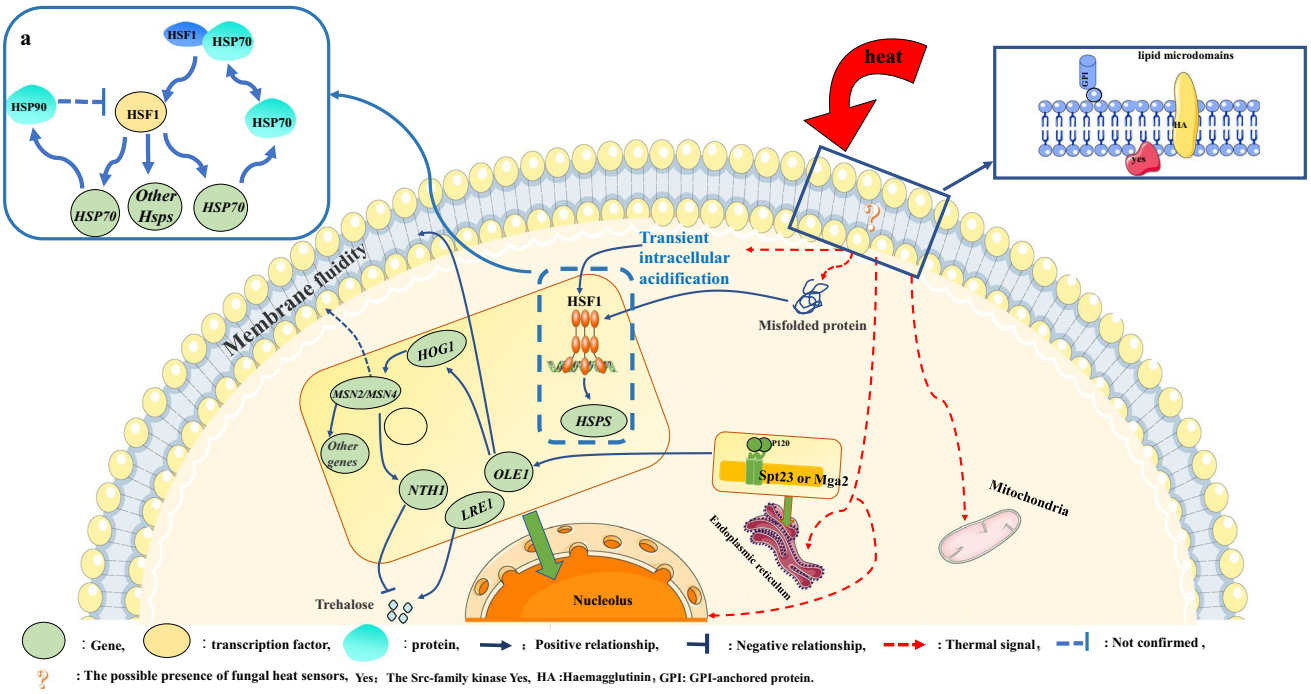

Fig. 3 Outline of the process of fungal thermal adaptation mechanism. The fungal cell membrane may be the first sensor of a sudden increase in external temperature; it subsequently transmits heat signals into the cell via lipid rafts and other substances that act as signaling molecules. After receiving a heat signal, cells control the expression of heat-resistance genes and secrete a variety of substances (such as heat shock proteins, trehalose, and glycerin) through the regulation of a series of transcription factors, thus helping cells resist the damage caused by heat stress. (a) When the concentration of unfolded proteins exceeds the capacity of Hsp70 at elevated temperature, Hsp70 is released from Hsf1, and the released Hsf1 induces more Hsp70. After sufficient Hsp70 is produced to restore protein homeostasis, Hsp70 binds and inactivates Hsf1. Experiments have indicated that Hsf1 expression is also inhibited by HS90 in vitro. However, further evidence is needed to explore the specific mechanism

and adaptation. We can further confirm central genes that play a major role in fungal responses to various stresses. Finally, these molecules can be used as targets to design effective drugs to combat pathogenic fungal diseases, in particular for antifungal and heat-resistant fungi.

Author contribution WX and ZYS conceptualized, wrote, and revised the manuscript. JPZ, JH, CYX, MJJL, and ZYS proofread it. All authors read and approved the manuscript.

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Declarations

Ethical statement This article does not contain any studies with human participants by any of the authors.

Conflict of interest The authors declare no competing interests.

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