Fungal thermal adaptation Fuels Human Pathogenic Fungal Diseases

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Abstract
Fungal diseases are a growing global health threat due to the increasing number of immunocompromised individuals and the emergence of drug-resistant fungal strains. Global warming has been profoundly reshaping the epidemiology of human fungal diseases, leading to a wider geographic distribution of pathogenic fungi (e.g., *Aspergillus*, *Cryptococcus*, and *Candida* species), increased virulence, and enhanced resistance to antifungal drugs. These phenomena are driven by the core mechanism whereby global warming enhances fungal thermal tolerance, equipping fungi with the ability to overcome mammalian thermal defenses, a key barrier to pathogenicity in humans. In this review, we have discussed how climate warming can exacerbate some major human fungal diseases (aspergillosis, cryptococcosis, and candidiasis) and also foster the development of drug-resistant strains. Furthermore, it examines emerging challenges and outlines strategic interventions on how to overcome them. Urgent action is needed to address the increasing threat of fungal diseases that will be caused by climate change. Such actions include enhanced surveillance, improved diagnostic tools, and novel antifungal therapies. These will be important to reduce the rising disease burden of human fungal diseases in a warming world.
Keywords: global warming, human fungal diseases, fungal thermal tolerance, mammalian thermal defenses, antifungal resistance, intervention strategies

1 Introduction

Fungal diseases have become one of the major threats to human beings in recent years due to the rising number of immunocompromised individuals as well as fungal drug-resistant strains[48]. Immunocompromised patients, such as those with acute myeloid leukemia, are more likely to suffer life - threatening fungal infections. These cases are still of great clinical importance despite the use of prophylactic antifungal treatments[64]. Certain diseases, such as aspergillosis or cryptococcal meningitis, highlight the need to develop better diagnostic methods and therapies. This is especially crucial in areas with higher prevalence[73], and also because of the development of resistance among fungal species, particularly in *Candida* species, which makes clinical treatment difficult to manage. The limited range of available antifungal agents and the emergence of drug resistance make new therapeutic options highly desirable [71].

Global warming generally refers to an ongoing increase in the global mean surface temperature, which has been primarily caused by anthropogenic emissions of greenhouse gases such as carbon dioxide (CO_2) and methane (CH_4)[1; 43; 46]. The Intergovernmental Panel on Climate Change (IPCC) estimates that average global surface temperatures have increased approximately 1°C above their late - 18th - century baseline values, and projections indicate a potential increase of 1.5°C as early as 2030 under continued emissions of pollutants[62]. All of these changes are having a major impact on the epidemiology of fungal diseases. Rising temperatures, along with an increased frequency of extreme climatic events, altered precipitation patterns, and intensified natural disasters, are modifying fungal growth, distribution, virulence, and resistance profiles. This is leading to a wider geographical spread of the fungal pathogen and a higher likelihood of newly susceptible immunocompromised patients being infected by more aggressive strains of fungus. [34; 61].

One of the main drivers for such changes is the increased thermal tolerance of fungi, thus enabling them to evade mammalian heat-shock responses, which are an important barrier for the establishment of infection. Here, we show that the present study systematically describes the major forms of human mycoses caused by global warming, assesses the adaptive response of fungal pathogens, and suggests specific strategies for countering it.

2 Global warming augments fungal thermal tolerance to override mammalian thermal defenses

Mammalian body temperature is an important host defence mechanism against pathogens, including fungi. Many fungi are not viable at body temperatures[59], which is possibly why our thermoregulatory system evolved in response to infections caused by these pathogens[6]. Rabbits can protect themselves from disseminated systemic cryptococcosis (caused by *Cryptococcus* species) due to their constant body temperature. However, cooler peripheral tissues such as the skin, mucosal surfaces, and genitalia are susceptible to infections[54]. The same temperature - related protective effect can be observed in bats. They are not infected with white-nose syndrome when they are active and warm - blooded in the summer, but become susceptible during the cold winters of hibernation when they cool down to a temperature range between 10°C - 12°C[53]. Similar temperature-dependent protection has been observed for amphibian immunity against Chytrid mycosis, where both prevention and therapeutic clearance are associated with elevated temperatures[60]. The application of these observations can be found, for example, in the treatment of

cutaneous sporotrichosis, where heat treatment is more efficient when the infection occurs in the extremities. Together, these data demonstrate that thermal defense is a conserved and critical element of the host's defense strategy against fungal infections.

Besides known thermal defense in mammals or other vertebrates, many studies have demonstrated that fungi can adapt themselves well when growing under high temperatures. Studies on heat resistance of the entomopathogenic species *Metarhizium anisopliae* showed enhanced mycelial growth at a body-temperature (37°C), a mechanism evolved in order to bypass the host's immunity response, which includes fever in the course of a mycosis[21]. Thermotolerance can often be rapidly evolved by microorganisms and may require relatively few mutations to achieve. For instance, thermotolerant variants of the yeast *S. cerevisiae* cultured at 42°C conditions exhibit which reported 153 mutations in total across 14 lab-passaged lineages[38].

Thermal tolerance, which determines the ability of fungi to infect warm-blooded animals, has evolved repeatedly across fungal lineages. It requires the dual functionality of sustaining cell growth at higher temperatures while rapidly adapting to large differences between ambient and body core temperatures. For example, in order to successfully infect human lungs, fungi would need to survive an instantaneous transition from variable ambient air temperatures, which vary from region to region, to a steady-state temperature field at 37°C in the human body. Specifically, for a fungus to colonize human lungs, it must be able to withstand abrupt changes between fluctuating ambient temperatures and the constant body temperature (37°C). This is a huge physiological challenge[10], as adjusting to new temperatures demands fundamental metabolic reprogramming, especially for species native to cold environments. Importantly, such temperature adaptation must occur rapidly to evade immune detection, as any delay could increase vulnerability to host defenses during these metabolically precarious transitional phases.

With the increasing threats of global warming, there has been a growing interest in understanding how pathogenic fungi will respond to rising temperatures. Such pathogens include species that only infect plants or poikilotherms, which may eventually evolve resistance to the heat of the human body and pose new threats. In particular, the almost simultaneous emergence of genetically heterogeneous *C. auris* clades in several countries worldwide over the last decade correlates with the increasing global temperatures and suggests that there may be an environmental selective pressure that facilitated the emergence of this pathogen in humans[11]. Furthermore, studies on the distribution of fungi show that their distribution is specialized to heat. There are more fungi in the tropics than elsewhere, and they cause more diseases under higher temperatures. Comparative studies between *Coccidioides* species have shown that these organisms prefer certain temperatures, which are associated with their natural habitat. Specifically, *Coccidioides posadasii*, a species that evolved in the Sonoran Desert, exhibits superior growth kinetics at 37°C compared to *Coccidioides immitis*, which is native to the temperate valleys of California[52]. The evolution of thermal tolerance has been observed over time according to recent studies on global warming and climate change. It has been demonstrated to increase the upper temperature thresholds of lab-cultivated populations from a *Basidiomycete* species[58]. Overall, these findings indicate a potential benefit of global warming to certain traits in fungi: increased intrinsic thermotolerance and/or enhanced capacity to adapt to higher temperatures; both traits may enhance the virulence mechanisms needed for infection establishment. (Figure 1).

3 Global warming could lead to the emergence of new fungal diseases

With the global intensification of climate warming and associated problems, it is quite possible that rising temperatures may lead to increased virulence of some fungi causing infectious diseases among humans; hence, new fungal diseases might emerge. The effects of temperature change on virulence are likely to be multifactorial, as they will impact the ecology and biology of fungi in numerous ways.

A further consequence of global warming is an expansion in the range of plant pathogens. Some fungal species might extend their geographical ranges into regions where they were previously absent because they are no longer restricted by temperature limitations and can thereby find suitable habitats, thus infecting human populations that were hitherto unexposed. For example, one possible effect of climate warming is to increase the range expansions of resident fungal pathogens in mammals (and, in addition, promote the development of heat - resistant strains via natural selection. Climate change is expected to transform the characteristics of currently harmless fungal species by removing thermal constraints on their development[33]. The spread of fungal infections may also be affected as rising temperatures modify the habitats of host species and disease carriers. As shifting climate conditions alter the territorial ranges of invertebrate organisms, their ability to serve as transmission agents for fungal infections changes accordingly[42].

Moreover, it is predicted that climate warming will also affect the virulence and antifungal resistance of plant pathogenic fungi. Temperature variations, rainfall patterns, and severe climate events can influence fungal proliferation, distribution, and virulence. Such changes may contribute to the emergence and/or dissemination of more virulent strains or those resistant to currently available antifungal drugs, posing serious challenges to disease management efforts[34].

4 Global warming accelerates the growth rates of *Aspergillus* species and alters their distribution

Elevated temperatures have been shown to enhance the growth rates of *Aspergillus* species, such as *Aspergillus niger*[19], which may, in turn, release more spores into the air as vectors for the transmission of aspergillosis. In Mediterranean countries, it has been shown that higher temperatures may accelerate chemical reactions and also increase the growth rate of microorganisms. Biofilm formation was also observed on the inner surface of pipes with relatively high counts (especially for *Aspergillus* species), suggesting that a warmer climate may have resulted in increased fungal proliferation inside distribution systems[22].A higher prevalence of *Aspergillus* species detected while flushing pipes implies that they are more likely to be found further, with a smaller thickness of the materials involved and probably higher temperatures favorable for growth. Additionally, independent research specifically examined the impact of temperature on the growth rate and biofilm formation of the thermally tolerant *Aspergillus flavus*[37]. The findings indicate an evident effect of temperature on conidiation on solid medium, as the best growth rate is obtained at 28°C, whereas high temperatures favor higher sporulation and concentrations. Moreover, it was found that a temperature of 37°C was optimal in terms of sporulation germination as well as biofilm formation by microorganisms.

A warming climate is predicted to increase the range expansion for some species of *Aspergillus*, raising the rates of diseases caused by aspergillosis in regions that historically had a low incidence[34]. *Aspergillus* species spores can produce toxic metabolites, for example, aflatoxins that pose a threat to human, animal, or agricultural

health[31]. Given the positive relationship between temperature and mycotoxin formation (especially in thermo-tolerant toxigenic fungi such as *A. flavus*)[2], we expect that climate warming may enable them to expand into areas where they have been limited by low temperatures, thereby expanding their niche. Other studies that investigated the effect of illumination and humidity on growth and aflatoxin synthesis in some strains of *A. flavus* and *Aspergillus parasiticus* demonstrated that an increase in the annual mean temperature associated with climate change may facilitate the spread of aflatoxin - producing fungi into areas that were formerly too cold[56]. For example, a 3 - year study of *Aspergillus* section *Flavi* (including *A. flavus* and *Aspergillus oryzae*) in French maize has revealed that the global distribution of aflatoxin B1, a mycotoxin produced by *Aspergillus* species, is undergoing alterations due to climate change[5]. Since 2015, the combination of spring droughts and warm summers has favored an increase in both the incidence of *Aspergillus* section *Flavi* within French maize fields, accompanied by a corresponding rise in aflatoxin contamination[5]. This suggests that global warming favors the colonization by *Aspergillus* species of new regions where these fungi were previously absent. In accordance with this statement, another study examining global patterns of species diversity and distribution within the fungal genus *Aspergillus* employed a random forest machine learning classifier to project the potential impacts of future climate change[57]. The findings indicate that while the response to climate change varies among different *Aspergillus* species, certain species, such as *Aspergillus versicolor*, could even expand their niche distribution[57]. In addition, these data further suggest that warming climates will facilitate the spread of *Aspergillus* species. Thus, populations living in tropical and subtropical areas could be more exposed to such fungal spores, possibly leading to an increase in the incidence of aspergillosis infections.

5 Global warming facilitates the growth and dissemination of *Cryptococcus neoformans*

Cryptococcosis is a severe opportunistic mycosis mainly caused by the fungus *C. neoformans*, affecting immunocompromised individuals and, although less frequently, immunocompetent people. Environmental factors (especially temperature) are important factors that influence the pathogenicity and virulence of *C. neoformans*. Higher temperature favors *C. neoformans*; *C. neoformans* will thrive and retain its virulence traits, where heat tolerance may increase the disease potential and survival within humans.

Global warming promotes the proliferation and dissemination of *C. neoformans* as it creates favorable environmental conditions for *the fungus*. This natural persistence plays a key role in the dissemination ability of this pathogen because it can survive under various conditions. The fungus persists in the environment, waiting for a suitable host to colonize[51].

When comparing *Cryptococcus deneoformans* and *C. neoformans*, *C. neoformans* strains survive better than *C. deneoformans* under high - temperature conditions (mammalian body temperature and fevers)[15]. This indicates that *C. neoformans has* evolved enhanced abilities to thrive at elevated temperatures, such as the body temperatures of mammals, which is consistent with our assumption that higher temperatures may be favorable to its growth. In an independently published study, it was shown that *C. neoformans* adapts to the mammalian body temperature by using Ccr4-mediated degradation of ribosomal proteins mRNAs. This thermotolerance property is important for growth and dissemination within the host's body. For instance, in the case of the *C. neoformans ccr4*Δ mutant, the authors

observed severely compromised thermotolerance capabilities.

In *C. neoformans*, heat - adaptation is known to induce drastic modifications in genes' transcriptional profiles under stress or increase the ability of alveolar macrophages to engulf the pathogen[7]. This suggests that this fungus has some inherent thermotolerance that allows it to avoid the immune system's clearance and facilitate its persistence within a mammalian host. In studies performed with birds, *C. neoformans* is able to grow at the bird's body temperature, which is significantly higher than mammalian body temperature. Avian macrophages are capable of limiting the intracellular proliferation of C. neoformans, but the ability to survive and replicate outside the host (at those temperatures) suggests that it can occupy a warmer niche[39], which may explain why this species is able to persist within avian hosts and potentially facilitate spread between environments through the avian reservoir. This finding regarding C. neoformans again highlights the role of temperature in its ecology and spread. Other studies have also shown that changes in the ambient temperature can dramatically impact *C. neoformans*, and temperature strongly influences the production of melanin, which is an important virulence factor for increasing the fungus's resistance against host immunity[44]. It has been observed that higher temperatures lead to faster development and increased prevalence of this fungus, thereby increasing its pathogenicity as well as its environmental stability.

6 Global warming may drive the evolution of more virulent *Candida* species

It is known that when the surrounding environmental temperature rises, the growth rate increases for some species of *Candida*. As a related example, there was an experiment on the effect of fermentation conditions on the number of white yeast colonies generated during kimchi fermentation. Three different incubation temperatures were tested: 4°C, 10°C, and 20°C during fermentation to observe their effects on the distribution of different yeasts such as *Candida sake*. The results showed that there were differences in the diversity and quantity of *Candida* species with respect to temperature, where certain species can dominate at different temperatures[41]. A second study focused on the enzyme - catalyzed synthesis of poly(glycerol sebacate) and investigated the influence of reaction temperature on the rate of polycondensation with *Candida antarctica* lipase B as the catalyst. When the reaction was performed in acetone between 30°C and 50°C, the observed reaction rate constant increased from 0.7 h^{-1} to 1.5 h^{-1}[55]. The relationship between increasing temperature and a faster reaction suggests that the enzymatic activities in the metabolism of *C. antarctica* are more active at high temperatures, which might lead to a higher rate of cell growth. The effect that this accelerated activity of enzymes at elevated temperatures will have on microbial growth is not clear.

Higher ambient temperature may also promote the virulence traits of the *Candida* strain itself. One such trait that increases the virulence of *C. albicans* is the production of germ tubes, for example, for tissue invasion and systemic infections. When observed by atomic force microscopy under ambient conditions, the growth rate of hyphae was found to vary significantly across a range of physiologically relevant temperatures[17]. Together, these findings suggest that temperature may have a direct effect on this critical virulence pathway of *C. albicans*, which could result in an increase in virulence at higher temperatures. Also, biofilm formation is a critical virulent property among pathogenic species of *Candida*. The effect of temperature on biofilm formation as well as attachment has been investigated for *C. albicans* and two additional strains of

Candida. It was shown that cells growing at the end of exponential growth (stationary phase) behave differently according to the temperature used for their cultivation[13]. Higher temperatures also have an effect on adherence and biofilm development and can lead to a greater ability for microorganisms to create a more defensive biofilm similar in nature to that seen during feverish states, which could enhance *C. albicans*' biofilm resistance. These biofilms form protective barriers to the host immune system and antibiotic treatment, thus increasing its virulence. In addition, the thermal environment regulates melanism levels in *C. albicans*, one of the factors related to increased fungal survival. In an analysis of Wor1 - dependent ferroxidases from *C. albicans,* it was shown that in rich growth conditions (YPD), activation of the Wor1 transcription factor induced the expression of most of the *FET*s but maximally induced four out of five *FET* genes at 37°C[18]. The induced *FET* genes are involved in the synthesis of dark pigments in opaque cells, and *C. albicans* strains containing melanin have increased survival rates. Overall, this indicates that temperature can affect virulence factors such as hyphae formation, and environmental conditions influence both biofilm formation and melanin production. In relation to global warming, these changes might also favor an increase in the occurrence and prevalence of more aggressive *Candida* species. These altered environments will likely select for more aggressive strains of fungi, thus creating novel problems in the clinic. The above example is a nice illustration of how microbes can respond to environmental changes and how these responses may have unintended consequences as climate change proceeds.

Global warming is conducive to the proliferation of *Candida* species. Among them, *C. auris* is one of the most concerning multidrug-resistant pathogens, which has emerged as an important clinical concern worldwide. The hypothesis of emergence from nature suggests that *C. auris* could be an environmental fungus before its isolation as a human pathogen, possibly acquiring human pathogenicity via heat - adaptive evolution in response to shifting climate regimes[11; 12]. The evidence in favor of this hypothesis is provided by studies on the emergence of *C. auris*, which suggest that climate warming could be contributing to the simultaneous and independent emergence of five clades in three geographical regions. Different from other *Candida* species, *C. auris* is more resistant to heat. It has been suggested that changing climate patterns caused the environmental progenitor of *C. auris* to adapt pathogen traits by responding to temperatures before it could spread globally via other hosts[32]. This evidence suggests that warming conditions are assisting in both the evolution and range expansion of this fungus. Other studies also support the idea that climatic change is contributing to the faster spread of *C. auris*. Together with the spread via travel and immigration to countries through the global health care system, it is likely that climatic changes are contributing to the worldwide distribution of this pathogen. Studies have shown that high ambient temperature is one of the factors contributing to an environment conducive to the growth of *Candida* species[47]. In South American hospitals, it was found that children had an increased incidence of *Candida* infection, particularly neonates compared to those in industrialized countries. The epidemic profile suggests that *C. auris* was identified as a cause of outbreaks among neonates and young children in Venezuela and Colombia[30]. Environmental changes, including rising temperatures, altered precipitation patterns, and extreme weather events, are leading fungal pathogens such as *C. auris* and *C. orthopsilosis* to adapt and respond to new climatic conditions[8]. These developments contribute to the

geographic spread of the fungus and thus also pose an increasing threat to human life. In conclusion, climate change will promote both the emergence of new species like *C. auris* and changes in the epidemiology pattern of candidiasis for different population segments.

7 Global warming contributes to the development of resistance in fungi

The emergence and increase in azole resistance among *Candida* species have also been associated with global warming, serving as a clear example of how climatic changes influence antimicrobial resistance profiles. Climate change has been found to play an important role in promoting fungal resistance to azole drugs[28; 29]. More alarmingly, however, it was found that *A. fumigatus* isolates resistant to azoles were more common at higher temperatures in greenhouses[72] or under tropical conditions[23]. While many factors are involved in the emergence of fungal resistance, areas characterized by a warm climate are often associated with a high prevalence of fluconazole - resistant *C. parapsilosis* isolates[20]. Most notably, it has been experimentally observed that the presence of thermal stress, such as growing microorganisms at a temperature of 37°C, can promote *C. albicans* resistance to azoles[27; 68; 70]. It has been proposed, therefore, that an interaction between high ambient temperature and resistance to azoles could occur, and they might have synergistic effects on fungal growth[63]. Furthermore, it seems that the worldwide appearance of multidrug - resistant *C. auris* isolates among humans is associated with the combination of adaptation processes caused by climate warming and exposure to antifungals.[3; 11].

Another hypothesis is that climate change could contribute to the emergence and dissemination of resistant *Candida* species, especially *C. auris*, which is emerging as a multi-drug-resistant nosocomial pathogen (thermal acclimation hypothesis). It posits that the fungus probably was already present in nature before it started causing disease, and that climate warming could have contributed to making it an emerging human pathogen. Evidence for the first possibility is provided by isolates of *C. auris* recovered from non - health care environments, showing that it occurs outside of health care settings. This suggests that warming climates may have allowed this species to become more heat - tolerant, thus increasing the virulence of this species[12]. In addition, different *Candida* species, such as *C. tropicalis,* have been reported to develop resistance against azoles, which are often used for *Candida* infections. The increasing prevalence and emergence of azole - resistant strains of *C. albicans* are of great concern to society. In general, environmental factors seem to be driving the increased emergence of resistance in the Asia-Pacific region. For example, genome analysis studies have shown duplication of genes or specific mutations leading to azole resistance in fast - growing populations of *C. tropicalis*, highlighting the urgency in developing strategies to combat the emergence and spread of drug - resistant fungi[25]. Given the complicated interactions that exist between climate warming and antifungal resistance patterns among *Candida species*, interventions need to be comprehensive, including climate monitoring, studies into the biological basis for developing resistance, and the application of interventions that will mitigate climate impacts on the spread of drug - resistant fungal diseases[40].

The link between elevated temperature and azole antifungal resistance (especially for *A. fumigatus*) has raised concerns in both clinical and environmental contexts. In recent times, an increasing number of cases of azole-resistant *A. fumigatus* isolates are being reported from different environments, where the environmental temperature plays an important role. High temperatures appear to favor the selection of resistant isolates as they provide a habitat that is more conducive to

their survival and proliferation compared with susceptible isolates. Studies conducted from 2020 to 2023 in Denmark revealed the environmental persistence of azole-resistant *A. fumigatus*. Common resistance-conferring mutations like TR34/L98H and TR46/Y121F/T289A were detected in most of the collected isolates. Resistant isolates were found to be widespread in the environment, especially in flower- and compost-related samples[4]. However, according to the literature, although strains of *A. fumigatus* resistant to azoles showed poor growth in the field environment, non-resistant isolates of *A. fumigatus* were effectively controlled by common azole fungicides, while these fungicides were ineffective against drug-resistant isolates. All of these findings indicate that specific environmental conditions, which may be exacerbated by climate warming, may unintentionally select for more prevalent resistant fungi within the soil community. This shows that antifungal resistance in fungi may also be affected by ecological interaction, emphasizing the great urgency to implement holistic approaches to combat and reduce the impact of azole resistance in warmer climates[4].

8 The mechanisms of fungal thermal tolerance

Thermotolerance in fungi is a consequence of a complex physiology, which encompasses molecular, genetic, and functional changes that work in tandem. It is a complex process involving sequential and interdependent responses. In this process, the production of defense molecules, heat shock proteins (HSPs), redox signaling systems, as well as a reconfiguration of metabolism, collectively establish thermotolerance.

8.1 Core Protective Molecules: Initiators of Thermal Defense

Trehalose is an important thermoprotective sugar that protects biomolecules against denaturation under high-temperature conditions. When the temperature rises, fungal species (such as *S. cerevisiae*) upregulate sugar transporter gene expression, resulting in higher amounts of produced trehalose. This sugar can bind both proteins and membranes, inhibiting their degradation and keeping them intact to prevent diffusion into the cytoplasm[50; 69]. For example, a study on *Zygosaccharomyces rouxii* showed that trehalose also protects against heat shock by inducing some stress-responsive genes. Thus, we have a self-amplifying system in which the presence of trehalose provides an immediate protective effect and, at the same time, activates long-term mechanisms for adapting to high temperatures[65].

The pyruvate serves as an immediate additional protection against the oxidative stress caused by heat. During heat stress, mitochondria produce high amounts of ROS, which impairs the ability to generate energy for cell survival. Fungi, including *Metarhizium robertsii* [67], oppose the effect by raising pyruvate concentrations to quench excess reactive oxygen species (ROS) and protect mitochondria. This key role in scavenging free radicals helps to maintain cellular homeostasis during high temperature stress and allows for the initiation of other defense mechanisms..

Spermidine/polyamines also enhance thermotolerance by modulating the metabolism of cellular ATP production. For example, in *Ganoderma lucidum*, spermidine can enhance the function of mitochondria and lipid beta-oxidation [35]. Thus, it can supply sufficient amounts of ATP for the operation of essential stress-response processes, such as the biosynthesis of trehalose and HSPs. In this manner, through their link between metabolism and thermotolerance, the polyamines assist in coordinating a global response of the fungus to stressful temperatures.

8.2 HSPs: Molecular Chaperones for Stress Recovery

HSPs are an important component of the

cell's protection mechanism. They act as chaperones to assist the refolding process of denatured or partially denatured proteins. All of these are evolutionarily conserved proteins that respond rapidly at the transcriptional level when ROS scavenging through trehalose or pyruvate metabolism occurs, setting up a unified response in which rapid stabilization of the structure is followed by global proteostasis surveillance[26; 67]. In *Histoplasma capsulatum*, it has been shown that Hsp60 interacts with several enzymes involved in metabolism as well as signaling pathways. This interaction can assist in the renaturation of denatured proteins due to temperature, thus maintaining important functions such as energy production or defense reactions within cells[35]. Analogously, in the pathogenic fungus *A. fumigatus*, the heat shock transcription factor HsfA integrates thermal signals and controls not only the expression of HSPs but also that of other genes involved in the integrity of the fungal cell wall[24]. These two processes must be coordinated because the recovery of protein structure by HSPs should coincide with the reinforcement of the cell wall to prevent lysis at elevated temperatures. Therefore, HSPs do not act in isolation; rather, they are part of a complex network that both restores the functionality of damaged proteins and supports cell integrity.

8.3 ROS Signaling: A Dual-Role Regulator of Adaptive Responses

ROS serves as both a stressor and a critical regulatory and protective signaling molecule during temperature tolerance in organisms. Appropriate ROS production under short-term thermal stress can activate a series of physiological response pathways[27]. For instance, in *Ganoderma lucidum*, heat-induced ROS enhances HSP synthesis and accelerates triterpenoid (ganoderic acid) production. This secondary metabolite stabilizes cell membranes and exhibits protective effects when combined with trehalose[45], thereby transmitting environmental stress signals to downstream pathways to confer resistance. Additionally, pyruvate and trehalose collaborate in regulating ROS levels: pyruvate reduces ROS concentration to prevent oxidative damage, while trehalose inhibits excessive ROS generation by suppressing ROS-producing organelles (such as mitochondria). This regulatory mechanism ensures fungi can utilize ROS signaling without toxicity, representing a sophisticated adaptive regulatory system.

8.4 Metabolic Reprogramming: Resource Allocation for Thermotolerance Maintenance

The response of fungi to heat treatment is basically based on a shift in metabolism from growth - related processes to those involved in heat tolerance. Upon heating, they divert metabolism away from anabolic pathways, such as cell growth and proliferation, to catabolic pathways used to fuel defense mechanisms. For example, the activation of spermidine-induced lipolysis to produce acetyl - CoA substrates required for trehalose biosynthesis and ATP needed for HSP expression is a consequence of ROS-regulated metabolic adaptation. This adaptation involves both suppressing genes involved in cell proliferation and activating enzymes responsible for cellular stress responses.

In conclusion, fungal thermotolerance involves an orchestrated set of steps beginning with: (i) trehalose and pyruvate providing immediate physical protection as well as reducing oxidant levels; (ii) the signal of reactive oxygen species (ROS) initiating the synthesis of heat shock proteins and altering metabolism; (iii) chaperones fixing unfolded proteins to restore their functions; and (iv) polyamines, along with the reprogramming of metabolism, sustaining ATP synthesis for further adaptations. These steps are tightly linked. Dysfunction of one

process (e.g., the synthesis of trehalose) has negative consequences for others (e.g., HSP - mediated protein refolding). Revealing how these associations act synergistically in conferring thermotolerance and with an understanding of this network, it will be possible for us to identify putative target points through which we can develop new antifungal drugs that target fungal heat-adaptation mechanisms.

9 Perspectives

The growing potential of fungi to threaten human health in a context of global warming demands continuing multidisciplinary work and anticipatory approaches. To mitigate risks, public health interventions and a research agenda that might be beneficial should be taken into account.

Build capacity to monitor and forecast weather influenced fungal diseases. This goal would be achieved by incorporating historical information about weather conditions (including extremes) into current disease monitoring systems so that they can forecast where and when outbreaks may occur.

Also, broadening environmental monitoring for resistant and heat - stable forms of fungi, especially in areas with rapid warming, will help identify emerging health risks in a timely manner and allow for prompt public health responses..

In addition, further elucidation of the molecular mechanism underlying fungal heat resistance is needed. Future investigations should aim to discover new physiological phenomena, such as DNA methylations and histone modifications, that are involved in fungal heat tolerance and pathogenicity[27]. Understanding such mechanisms would help identify new drug targets against fungi. This knowledge can be exploited in the design of specific treatments aimed at hindering the ability of fungi to adapt to higher temperatures, including agents that prevent the action of heat shock proteins or inhibit pathways leading to trehalose synthesis.[49; 67].

Third, we need to implement effective prevention and control measures in a “One Health” manner[14]. Since most of the human fungal pathogens are environmentally sourced, interventions will need to be multifaceted, addressing human, animal, and environmental issues concurrently. Controlling the animals that host the fungi is one aspect of this approach. For example, dealing with bird - borne *C. neoformans*[16], as well as interrupting transmission chains by improving hygiene in vulnerable areas during disasters. Additionally, it also involves integrating adaptation to climate change, such as reducing greenhouse gas emissions, and strategies to mitigate the spread of invasive species or pathogens. .

Fourth, the war on antifungal drug resistance must begin today by improving our current antifungals and also investing heavily in new ones that target drivers of resistance, such as climate change (e.g., temperature - dependent azole resistance)[27; 66]. Furthermore, the development of alternative strategies, including RNA - based drugs[9] or biological control using microbes, may offer sustainable alternatives to conventional antifungal treatments.

Global cooperation and global capacity building are also crucial because mycoses represent a global public health issue: fair distribution of diagnostic, treatment, and monitoring information, particularly among the populations of developing countries, which are more vulnerable to climate-related disease impacts. Developing international partnerships to share information on the standardization of clinical trials and develop local health care resources is an important part of dealing with this worldwide problem.

In summary, integrated efforts to address climate change, mycology, and public health are necessary if we hope to mitigate risks in the coming years. In particular, with regard to surveillance, basic research, broad - based

prevention strategies, and antimicrobial resistance management, international collaboration will lead to the development of solutions that protect human health in an increasingly warming world.

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Conflicts of Interest

The authors declare no competing interests.

Author contributions

Bicheng Jiang and Hui Lu wrote the manuscript draft. Wanqian Li and Yuanying Jiang revised the manuscript. Hui Lu and Yuanying Jiang conceived the idea.

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Figure legends

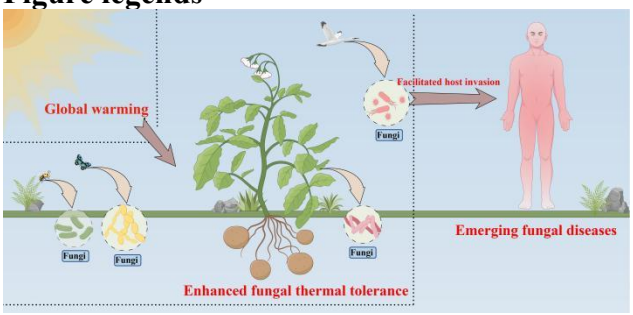

Figure 1. Global warming is likely to exert selective pressure that enhances the baseline thermal tolerance of fungi and accelerates their adaptive responses to heat stress within the host. Collectively, these adaptations may augment virulence mechanisms that are essential for successful host invasion[10; 11; 36].