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MINI-REVIEW

# *Aspergillus fumigatus* escape mechanisms from its harsh survival environments

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## Abstract

*Aspergillus fumigatus* is a ubiquitous pathogenic mold and causes several diseases, including mycotoxicosis, allergic reactions, and systemic diseases (invasive aspergillosis), with high mortality rates. In its ecological niche, the fungus has evolved and mastered many reply strategies to resist and survive against negative threats, including harsh environmental stress and deficiency of essential nutrients from natural environments, immunity responses and drug treatments in host, and competition from symbiotic microorganisms. Hence, treating *A. fumigatus* infection is a growing challenge. In this review, we summarized *A. fumigatus* reply strategies and escape mechanisms and clarified the main competitive or symbiotic relationships between *A. fumigatus*, viruses, bacteria, or fungi in host microecology. Additionally, we discussed the contemporary drug repertoire used to treat *A. fumigatus* and the latest evidence of potential resistance mechanisms. This review provides valuable knowledge which will stimulate further investigations and clinical applications for treating and preventing *A. fumigatus* infections.

### Key points

- *Harsh living environment was a great challenge for A. fumigatus survival.*
- *A. fumigatus has evolved multiple strategies to escape host immune responses.*
- *A. fumigatus withstands antifungal drugs via intrinsic escape mechanisms.*

**Keywords** *Aspergillus fumigatus* · Aspergillosis · Escape mechanisms · Immunity responses · Microecological agents · Drug resistance

## Introduction

*Aspergillus fumigatus* is the main pathogenic fungus underlying aspergillosis and globally causes more than 300,000 life-threatening infections every year (Earl Kang and Celia 2021). Moreover, in recent years, during the Coronavirus 2019 (COVID-19) pandemic, pulmonary aspergillosis led to *Aspergillus* co-infections with COVID-19 developed into a clinical, major life-threatening fungal disease (Giacobbe et al. 2022; Hoenigl 2021). As a saprophytic fungal pathogen, *A. fumigatus* proliferates via abundant, small diameter (2–3 μm), air-borne asexual conidia. Although the fungus may encounter harsh natural conditions, such as high temperatures, poor carbon or nitrogen sources, ultraviolet light, and reduced metal ion levels, it has evolved adaptive survival systems. Generally, conidiophores generate thousands of conidia; indoor and outdoor airborne conidia concentrations can range from 1 to 100 conidia/$m^3$ and even reach up to $10^8$ conidia/$m^3$ in certain environments (Latgé and Chamilos 2019). Moreover, abundant conidia are inhaled daily into

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human lungs (Furlong-Silva and Cook 2022). In immunocompetent hosts, approximately 90% of inhaled conidia are swiftly cleared at mucosal surfaces and ciliated cells in the respiratory tract. Residually activated and swollen conidia face hostile environments, including low carbon sources, low oxygen concentrations, and host immune responses (Margalit and Kavanagh 2015); therefore, *A. fumigatus* survival in healthy individuals poses challenges to the fungus. However, *A. fumigatus* can evade host defenses for the spores to germinate or proliferate and causes aspergillosis in immunocompromised and immunodeficient individuals (Verburg et al. 2022).

When *A. fumigatus* breaks through host airway defenses and accesses the lungs, a chain reaction of antifungal host responses is activated. For example, germinating conidia may be phagocytized by alveolar macrophages (AMs) while germ tubes are quickly and effectively targeted by neutrophils (Ortiz et al. 2022). However, several complex fungal regulatory systems, such as altering recognition receptors, releasing reactive oxygen species (ROS) detoxifying enzymes, as well as biofilm and aspergilloma development, have been evolved to cope with the host immune responses (Latgé and Chamilos 2019). *A. fumigatus* also appears to co-operate with viruses, bacteria, and fungi to facilitate multiple colocalization sites that augment *A. fumigatus* invasion and its seriousness. Currently, *A. fumigatus* is mainly treated using azoles, echinocandins, and polyenes. Especially the itraconazole, voriconazole, isavuconazole, and posaconazole were the primary treatment drugs (Ben-Ami 2023). However, with long-term drug use, drug-resistant strains can survive via targeted protein overexpression or mutation, efflux pump overexpression, and altered mitochondria-related the high-osmolarity glycerol (HOG)-mitogen-activated protein kinase (MAPK) signaling and Heat Shock Protein (Hsp)90-calcineurin pathways. Therefore, *A. fumigatus* infection requires serious clinical attention.

In this review, recent research progress on *A. fumigatus* and its ability to confront negative factors in the natural environment, host defenses, and other lung-colonizing microorganisms are outlined. Importantly, fungal adaptation mechanisms, incorporating perception, regulation, response, and adaptation processes, are examined. Also, current fungal therapies and major fungal drug resistance mechanisms are discussed. This review could provide valuable insights on *A. fumigatus* infection prevention and treatment measurements.

## Fungal adaption in the natural environment

*A. fumigatus* is ubiquitous in external environments, including soil, decaying vegetation, and air, and has evolved many regulatory mechanisms to adapt growth to different factors (temperature, pH, carbon and nitrogen sources, and metallic ions). *A. fumigatus* grows and survives in extreme environments in temperatures up to 70 °C by exploiting multiple temperature regulatory systems (Hokken et al. 2023). In 2010, *A. fumigatus* proteome alterations during 30–48 ℃ shifts were examined by mass spectrometry and showed that Hsp30, Hsp42, and Hsp90 proteins were highly elevated after heat shock (Albrecht et al. 2010). Hsp90 is a conserved and essential eukaryotic molecular chaperone; it mediates proteostasis to avoid protein damage and misfolding during hyperthermy (Hervás and Oroz 2020). Hsp90 also interacts with cell wall integrity pathway (CWIP) components which are crucial signaling pathways maintaining cell viability under thermal stress (Crunden and Diezmann 2021). With the temperature increase, Hsp90 could interact with the CWIP component MAPK to prevent its aggregation (Rocha and Minari 2021). Furthermore, *hsp* expression is regulated by heat shock transcription factors (HSFs). Under stress, HSF factor 1 (Hsf1) homotrimers bind to specific DNA motifs or heat shock elements in target gene promoters to induce thermal adaptation gene expression, such as Hsp90 and Hsp70. Hsp90 also regulates Hsf1 activity by binding to the Hsf1 feedback regulatory loop to maintain its inactive state under normal conditions (Fabri et al. 2021). Additionally, many other genes are reportedly involved in *A. fumigatus* thermotolerance regulation, e.g., a putative α-1,2-mannosyltransferase deletion strain exhibited thinner hyphal cell walls when compared with the parental strain at 48 ℃. The thermotolerance gene *thtA* was essential for *A. fumigatus* growth at 48 ℃, while a *thtA* deletion mutant was more sensitive at this temperature when compared with the original strain (Chang et al. 2004; Wagener et al. 2008). Thermotolerance regulated genes from the literature are summarized (Table 1).

Nutrients are essential for *A. fumigatus* survival as the fungus has evolved highly sophisticated homeostatic mechanisms to respond to, take up, recycle, and use many varied nutrients. In the natural environment, nitrogen predominantly occurs in inorganic forms: atmospheric nitrogen, ammonia, nitrite, and nitrate. As a nitrogen sensor in *A. fumigatus*, rapamycin (TOR) protein was crucial for this fungal, and the gene missing mutant was more sensitivity and deficits in germination ability on poor nitrogen medium compared to wild strains. TOR promoted GLN3 (promoted GATA transcription factor) binding to cytoplasmic protein URE2 to control cytoplasmic protein synthesis and degradation under nitrogen-limited conditions (Baldin et al. 2015; Beck and Hall 1999). The Ras-related gene *rhbA* deletion mutant exhibited TOR kinase inhibitor rapamycin hypersensitivity and also had significantly reduced growth rates on poor nitrogen-sources (Panepinto et al. 2003). The *brlA* gene ($C_2H_2$ zinc finger transcription factor) deletion mutant exhibited downregulated gene expression encoding ribosomal proteins under nitrogen-limiting conditions; however,

**Table 1** Genes and proteins related to *A. fumigatus* ability to withstand adverse natural conditions

| Gene | Protein annotation | The biological function | Phenotypic deficiency of gene deletion or repression | References |
|---|---|---|---|---|
| Thermotolerance | | | | |
| *afpmt1* | O-mannosyl-transferase | Necessary for growth above 37 °C | The gene mutant had defect in growth and the conidial formation at 48 °C | (Wagener et al. 2008) |
| *cgrA* | Nucleolar protein | Affect the growth at 37 °C | The deletion *cgrA* mutant showed nucleolar protein NopA was delocalized in the nucleolus at 37 °C | (Bhabhra et al. 2006) |
| *that* | Unknown | Essential for growth at 48 °C | Deletion mutant had the temperature sensitivity | (Chang et al. 2004) |
| *hsp90* | Heat shock protein | Connecting point between thermotolerance and stress response | Deletion mutants were defective in the phenotype of spore viability, hyphal growth, germination, and conidiation | (Rocha and Minari 2021) |
| *pkcA* | Protein kinase C | Affect the growth or germination above 37 °C | The gene mutant altered the genes expression related to cell wall | (Rocha et al. 2015) |
| *afBck1*, *afMkk2*, *afMpkA* | Three-component mitogen-activated protein kinases | Essential for growth at 37 °C | Deletion mutants showed the growth and hyphal morphology, alkaline pH, and oxidative stress sensitivity in the mutant | (Dirr et al. 2010) |
| *rlmA* | Component of the cell wall integrity pathway | Influence the growth and germination above 37 °C and the tolerance to oxidative damage | The gene mutant altered cell wall organization and showed the defects of vegetative growth and tolerance to cell wall-perturbing agents | (Rocha et al. 2016) |
| *hsfA* | Heat shock transcription factors | Interaction with the main players of the CWI and HOG pathway | No report | (Fabri et al. 2021) |
| *rho1*, *rho2*, *rho4* | Rho GTPases family | Affect the growth at 48 °C | The deletion mutants reduction of β-1,3-glucan and glucosamine moieties on the cell wall and showed cytoplasmic leakage | (Dichtl et al. 2012; Zhang et al. 2018) |
| Nitrogen or carbon acquisition | | | | |
| *tor* | Tor kinase | Governs cell growth and proliferation in response to nutrient availability | Deletion strains are inviable | (Sun et al. 2022) |
| *areA*, *areB* | GATA transcription factors | Response for the utilization arginine as a nitrogen and carbon source | The deletion mutant reduced levels of NADP-GDH enzyme activity on ammonium | (Macios et al. 2012) |
| *leuB* | Leucine transcriptional activator | Involved in BCAA biosynthesis, nitrogen metabolism, and iron acquisition in vitro and in vivo | The deletion mutant showed growth defect and can be cured by supplementation with leucine or iron | (Long and Orasch 2018) |

**Table 1** (continued)

| Gene | Protein annotation | The biological function | Phenotypic deficiency of gene deletion or repression | References |
|---|---|---|---|---|
| *leuA* | α-isopropylmalate isomerase | Involve in the leucine biosynthetic pathway | The deletion mutant increased leucine dependence and<br>The deletion mutant decreased virulence in an insect infection model | (Orasch et al. 2019) |
| *leuC* | α-isopropylmalate synthase | Involve in the leucine biosynthetic pathway | The deletion mutant increased leucine dependence and rendered avirulent in a pulmonary aspergillosis mouse model | (Orasch et al. 2019) |
| *rhbA* | Ras-like signaling protein | Sensing different nitrogen sources | The gene mutant was impaired in poor nitrogen sources | (Panepinto et al. 2003) |
| *cpcA* | Transcriptional activator | Regulate the cross-pathway control system of amino acid biosynthesis | The gene mutant showed no growth in amino acid starvation | (Krappmann et al. 2004) |
| *cpcC* | The CPC system member | Regulate the cross-pathway control system of amino acid biosynthesis | The deletion mutant showed hyphal extension and sporulation was growth slowly when amino acid starvation | (Sasse et al. 2008) |
| *met8* | The bifunctional dehydrogenase/ferrochelatase enzyme | Affect the synthesis of siroheme for nitrite and sulfite reductases | The gene mutant was inability to utilize sulfate and nitrate as sulfur and nitrogen sources | (Dietl et al. 2018) |
| *sakA* | MAP kinase pathway | Involved in nutritional sensing, and to be activated upon starvation for carbon or nitrogen during vegetative growth | The gene mutant was more sensitive to osmotic, oxidative stresses and cell wall damaging agents, as well as had a 40% reduction in fungal burden in murine model | (Xue et al. 2004) |
| *gprK* | G-protein-coupled receptor | Function in external carbon source sensing | The deletion mutant was hyper-activation of germination the carbon limitation and showed reduced tolerance to oxidative stress | (Jung et al. 2016) |
| *sho1p*, *msb2p*, and *opy2p* | Hog1p upstream signaling receptor in HOG/CWI pathways | Regulate sugar storage | The gene mutant altered trehalose and glycogen accumulation | (Silva and Frawley 2020) |
| *FacB* | Transcriptional activator | Utilization of extracellular carbon source glucose and acetate | The gene mutant showed growth defects in the acetate as the only carbon | (Ries et al. 2021) |
| Fe acquisition | | | | |
| *sidA*, *sidC*, *sidD/sidF*, *sidG* | Produces four siderophores | Iron acquisition regulation | The deletion mutants were complete dependence upon reductive iron assimilation for growth under iron-limiting conditions | (Schrettl et al. 2007) |
| *sreA*, *hapX* | Transcription factors | Iron acquisition regulation | The deletion mutants were increased sensitivity to iron | (Schrettl et al. 2008) |

**Table 1** (continued)

| Gene | Protein annotation | The biological function | Phenotypic deficiency of gene deletion or repression | References |
|---|---|---|---|---|
| *amcA* | Mitochondrial transporter AmcA | Putative mitochondrial carrier for siderophore precursor ornithine | The gene mutants were increased the susceptibility to the polyamine biosynthesis inhibitor eflornithine and mitochondrial ornithine import | (Schafferer et al. 2015) |
| *acuM*, *acuK* | Zinc cluster transcription factor | AcuM suppresses *sreA* and induces *hapX* to stimulate expression of genes for reductive iron assimilation and siderophore-mediated iron uptake | The deletion mutants impaired capacity to grow under iron-limited conditions and gluconeogenic carbon sources | (Pongpom et al. 2015) |
| *ansrbA* | Sterol regulatory element binding proteins, basic helix-loop-helix transcription factors | Mediates regulation of iron acquisition in response to hypoxia and low iron conditions | The gene mutant was increased sensitivity to iron starvation and hypoxia | (Blatzer et al. 2011) |
| *cccA* | Vacuolar iron importer | Related to the iron detoxifying mechanism of vacuolar | The deletion mutant decreases iron resistance for depressed iron uptake | (Gsaller et al. 2012) |
| Zn acquisition | | | | |
| *zrfA*, *zrfB*, *zrfC*, *zrfD*, *zrfE*, *and zrfH* | Zinc transporte | Regulate zinc transport | The deletion mutant decreased growth in Zn-limitation acid conditions | (Robinson et al. 2021; Vicentefranqueira et al. 2015) |
| *zafA* | Transcriptional activator | Regulates zinc homeostasis | The deletion mutant decreased growth in Zn-limitation acid conditions | (Vicentefranqueira and Amich 2018) |
| *pacC* | Transcriptional regulator | Repression of *zrfA* and *zrfB* in neutral and alkaline, zinc-limiting media | The deletion mutant reduced significantly in alkaline zinc-limiting media | (Toledo et al. 2022) |
| *aspf2* | Zinc transporter-encoding genes | Expressed in alkaline and zinc-limiting conditions for fungal growth | The gene mutant reduced growth capacity under zinc-limiting conditions | (Amich et al. 2010) |

the mutant was insensitive to a TOR inhibitor, suggesting that *brlA* was not downstream of TOR signaling (Twumasi-Boateng et al. 2009). Furthermore, the stress-activated protein kinases (SakA)/HogA MAPK pathway was activated upon nitrogen starvation during vegetative growth (Ma and Li 2013). SakA is part of the nitrate and nitrite assimilation cascade during fungal germination processes. When compared with the wild-type stain, the *sakA* defective mutant showed increased germination rates on limited nitrogen medium and demonstrated that MAPK negatively regulated conidial germination (Perez-Cuesta and Guruceaga 2021). Other major uptake and metabolic gene regulators of non-favored nitrogen sources include the zinc finger transcription factor GATA-like genes *areA* and *areB*. *AreA* controls the expression of the glycosylphosphatidylinositol-anchored protein SwgA, which is localized to membranes and is involved in germination, growth, and morphogenesis (Samalova et al. 2023). On primary nitrogen sources, AreA interacts with NmrA protein (nitrogen metabolite repression compound) to inhibit the induction of secondary nitrogen sources (Andrianopoulos et al. 1998). However, when primary nitrogen sources are not present, *tamA* (Zn(II)2Cys6 transcription factor) interacts with *areA* to activate nitrogen catabolism (Downes et al. 2014). *AreB* is generally regarded as a negative nitrogen metabolism regulation factor, and AreB expression depends on AreA and AreB to negatively regulate AreA-dependent nitrogen catabolic gene expression under nitrogen-repressing or starvation conditions (Macios et al. 2012). Additionally, GcnE (acetyltransferase (Lin et al. 2020)), RgsC (G-protein signaling protein(Kim et al. 2017)), and Met6 (a bifunctional dehydrogenase/ferrochelatase enzyme (Dietl et al. 2018)) may also be involved in nitrogen metabolism; however, little is known about these processes. The regulatory genes responsible for *A. fumigatus* growth on different nitrogen sources are summarized (Table 1).

Environmental fungi carbon sources mainly include glucose, lactate, and acetate. Glucose is the most favored carbon source for fungal survival and niche colonization. It was reported that the G-protein coupled receptor system and the hexose transporter are required to sense and uptake glucose (Qadri et al. 2021; Ries et al. 2018). For example, a member of this family GprK was characterized as a carbon-sensing receptor in *A. fumigatus*. Gene loss mutants showed increasing germination rates under carbon starvation and growth restriction levels on a medium containing a sole carbon source (pentose) (Kim et al. 2017). Also, HOG/CWI pathways were implicated in carbohydrate metabolism. The Hog1p upstream signaling receptors Sho1p, Msb2p mucin, and Opy2p genetically interacted, while their null mutants showed altered trehalose and glycogen accumulation, suggesting regulated sugar storage by the HOG/CWI pathway (Silva and Frawley 2020). Another system called Carbon Catabolite Repression showed preferences for glucose or preferred sugars. The $C_2H_2$ zinc-finger transcription factor *creA* and the regulatory controller *facB* were available for extracellular glucose and acetate utilization (Ries et al. 2021). Genes related to carbon source regulation are summarized (Table 1).

Metal ion metabolism affects almost all *A. fumigatus* biological functions, including fungal virulence, cell wall integrity, azole susceptibility, protein phosphatases, antigen secretion, signal transduction, and even mitochondrial functions (Blatzer and Latgé 2017). During iron shortages, *A. fumigatus* generally increases expression of *hapX* (bZip CCAAT-binding transcription factor), *sidA* (ornithine monooxygenase), and *mirB* (siderophore transporter), while down-regulating *sreA* (GATA transcription factor), *cccA* (vacuole iron importer), and *cycA* (cytochrome C) during iron abundant conditions to maintain iron homeostasis (Matthaiou et al. 2018). Under iron starvation, HapX interacts with the CCAAT-binding core complex to activate iron acquisition and siderophore transporters, repress iron-consuming processes, and the vacuolar iron transporter pathway (Schrettl et al. 2010). During iron excess, SreA represses *hapX* expression, represses iron uptake, and promotes its use (Wiemann et al. 2014). Similarly, in the case of excess iron, the intracellular siderophore ferricrocin and vacuole was important to detoxification, and the vacuole iron importer encoding gene *cccA* deficiency decreases iron resistance (Gsaller et al. 2012). Also, the leucine biosynthetic and signal-transduction pathways, phosphatase Z and TOR kinases, are reportedly required during adverse iron conditions (Orasch et al. 2019).

Zinc is essential for fungal growth, and zinc homeostasis in *A. fumigatus* is regulated upon the external condition. During zinc affluent conditions and to transport redundant zinc to extracellular spaces or vacuoles for detoxification, *aceA* (transcription factor) induces *crpA* ($Cu^+$ P-type ATPase) and *zrcA* (vacuolar zinc transporter) expression (Cai et al. 2018). Under zinc-deficient conditions, *ZafA* (transcriptional activator) up-regulates *ZrfA* and *ZrfB* (zinc transporters) in acidic or neutral conditions, while in the alkaline with calprotectin, it mainly up-regulated *ZrfC* to reduce zinc consumption (Amich and Calera 2014; Amich et al. 2009). Additionally, *ZrfA*, *ZrfB*, and *ZrfC* expression is further modulated by *PacC* (transcription factor) depending on ambient pH (Toledo et al. 2022). *ZafA*-mediated fungal growth regulation is also influenced by iron availability, which is enhanced in zinc- and iron-repleted media, but growth is restricted by reducing zinc intake under iron starvation (Vicentefranqueira et al. 2019). Metal ion metabolism genes are summarized (Table 1).

Thus, *A. fumigatus* has developed several effective mechanisms to survive adverse conditions and combat stress-related changes. It was reported that more than 80 *A. fumigatus* strains have been isolated from Arctic soils

(Korfanty et al. 2021). Apart from normal regulatory mechanisms (temperature, carbon, nitrogen, and metal ion acquisition), several highly coordinated adaptation mechanisms are also used to exploit other external environmental conditions. For example, *A. fumigatus* can be grown in 5% carbon dioxide, very low pH (3.5), and under ultraviolet radiation. Proteome analyses have shown that stress responses, including cell wall reorganization, DNA repair, and oxidative stress responses during citric acid and itaconic acid production, are increased to overcome radiation effects (Alonso et al. 2017; Oliveira et al. 2021). However, these data constitute only a small component of *A. fumigatus* survival mechanisms. When *A. fumigatus* is inhaled into the human body, it faces a more complex internal environment.

## *A. fumigatus* survival strategies in hosts

When *A. fumigatus* conidia invade organisms, they become metabolically active and swell. To quickly clear spores, host responses are physically initiated via mucosal surface barriers in the respiratory tract. On epithelial surfaces in upper and lower respiratory tracts, most conidia are trapped in mucus and removed via ciliated cell actions (Crossen and Ward 2022). In healthy individuals, mucociliary clearance and phagocytic defenses normally prevent fungal-associated diseases; thus, *A. fumigatus* isolation from respiratory secretions in normal hosts generally reflects colonization rather than infection (Gago et al. 2019). However, in immunocompromised hosts, *A. fumigatus* can attach to sinonasal epithelial cell monolayers to form three-dimensional biofilm structures with parallel-packed, cross-linked hyphae and channels to induce sinusitis or tracheobronchitis (Singhal et al. 2011). Consequently, conidia breakdown barriers to reach the lower respiratory tract, and compromised lung epithelia provide an entry portal for fungi (Bertuzzi et al. 2018). In alveolar epithelium, epithelial cells covering over 95% of inner alveolar surfaces function as efficient *Aspergillus* conidia neutralizers via actin-dependent phagocytosis in mature acidified phagolysosomes or by endocytosis induced by protein–protein interactions between the host and pathogen (Latgé and Chamilos 2019). For example, lung mucin glycoproteins contain twelve binding sites for fucosylated structures and avidly bind to FleA (lectin), which is expressed by *A. fumigatus*, while integrin $\alpha_5\beta_1$ interacts with *A. fumigatus* CalA (thaumatin-like protein) (Liu et al. 2016; Richard et al. 2018). However, most pathogens control host innate immune responses at early stages, before infiltrating host immune cells arrive at infection sites. For example, *A. fumigatus* Aspf2 (factor H-binding protein) blocks host innate immune attack at early infection stages. Similarly, to avoid C3b complement system activation, *A. fumigatus* recruits several human plasma regulators (factor H, factor-H-like protein 1, and factor H-related protein 1). Aspf2 also recruits plasminogen to damage human lung epithelial cells, induce cell retraction, and expose the matrix. Therefore, when *A. fumigatus* is not phagocytosed, tissue is penetrated (Dasari et al. 2018). High-resolution live-cell confocal microscopy assays have indicated that *A. fumigatus* spores could survive from the maturation failure phagosome (about 60%), and the hyphae would fused to the host plasma membrane rather than rupture the phagolysosomal membrane to allow it growth better. Then, hyphae escape from epithelial lung cells in a non-lytic manner and elongate to adjacent cells without penetrating the host cytoplasm (Seidel et al. 2020). And the dihydroxynaphthalene (DHN)-melanin, the additional layers in the outer part of the conidia cell wall, was one of the interference factors for host endocytosis. Proteomics analyses of *A. fumigatus* conidia-containing phagolysosomes have shown that melanin inhibits phagolysosome acidification, Rab5- and Vamp8-mediated endocytic trafficking, and cathepsin Z (lysosomal cysteine protease) recruitment. Therefore, melanin promotes conidia germination and escapes from AMs via hyphal growth (Amin et al. 2014). Melanin is also involved in fungal adhesion and biofilm formation, enhanced fungal immune tolerance, and decreased exposure to pathogen-associated molecular patterns (PAMPs) to limit phagocyte phagocytosis. A recent study reported that melanin also removed chemokines (CXCL10 and CCL20) to suppress host inflammatory responses (Graf et al. 2023).

Due to continuous inflammatory response activation during *A. fumigatus* infection, pulmonary would appear local tissue hypoxia (Gago et al. 2019). As oxygen is essential for *A. fumigatus* biochemical processes, the fungus adapts to oxygen limitations. Transcriptomic and proteomic analyses have shown that during glycolysis induction, the transcriptional down-regulation of the tricarboxylic acid cycle and oxidative phosphorylation processes are major hypoxia-response measures. Transcripts were associated with iron and sterol metabolism, the cell wall, and GABA shunts, which were significantly increased to cope with stress (Barker et al. 2012). It was reported that TcsC (Group III two-component sensor kinase) was required for adapting fungi to low oxygen levels. Low oxygen caused TcsC-dependent phosphorylation of SakA, and the *ΔtcsC* mutant was susceptible to increased morphogenetic changes (McCormick et al. 2012). Similarly, mitochondrial respiration is also critical for fungal pathogenesis during hypoxia. In a mouse model, the mitochondrial respiration chain component *cycA* (cytochrome C gene) and *alcC* (alcohol dehydrogenase gene) deleted strains have been come out the defect virulence (Grahl et al. 2012, 2011). Chromatin immunoprecipitation followed by parallel DNA sequencing showed that *SrbA* (sterol regulatory element-binding protein gene) helped regulate ergosterol biosynthesis and iron uptake during hypoxic conditions or iron limitation (Zhang

et al. 2021a). Critically, the lung is a "sponge," and there are not enough carbon or nitrogen sources on lung surfaces to limit *A. fumigatus* growth. Therefore, *A. fumigatus* generates proteases (serine proteases, metalloproteinases, and aspartic proteases) to decompose organic components (Abad et al. 2010). Besides these genes above-mentioned about the carbon and nitrogen metabolism, the transcription factors are also important for *A. fumigatus* survival in vivo. For example, *facB* (transcription regulatory factor required for acetate utilization) is essential for carbon metabolism in vivo. A *facB* deficient strain showed significantly reduced virulence in both *Galleria mellonella* and murine invasive pulmonary aspergillosis (IPA) models (Ries et al. 2021). During mold infection, amino acid biosynthesis is required for nitrogen metabolism. The *cpcA* gene encodes the transcriptional activator of the cross-pathway control system (CPC) of amino acid biosynthesis. Indeed, a *cpcA* deletion strain not only impaired the CPC system in terms of amino acid starvation, but also attenuated virulence in pulmonary aspergillosis mice (Krappmann et al. 2004).

## Escaping immune responses

After *A. fumigatus* evades the host's upper respiratory tract, it can survive on lung surfaces where conidia germinate and form invasive hyphae which penetrate pulmonary tissues and enter alveoli. AMs are first-line innate host defenses and use pathogen-recognition receptors (PRR) and PAMPs. Toll-like receptors (TLRs) are a major PRR class responsible for activated innate immune responses, especially TLR2 and TLR4, which recognize fungal PAMPs, including, peptidoglycans, RNAs, zymosan, lipopolysaccharide, and HSPs (Kumar 2022). However, the TLR4 induces signals were responding just in the stimulation of conidia, while *A. fumigatus* germinates into hyphae, the TLR4-mediated signaling would be loosed (Netea et al. 2003). Thus, the main effects of proinflammatory cytokines come from TLR2-activated non-protective Th2 (T-helper 2) responses (Buckland et al. 2008). Meanwhile, the *Aspergillus* gliotoxin produced by *A. fumigatus* could target the host cell phosphatidylinositol 3,4,5-trisphosphate [PtdIns(3,4,5)P3] metabolism to break the phagocytes protective functions, so that this pathogen could escape the macrophage recognition and downregulating phagocytic immune defenses (Schlam et al. 2016). Macrophages and neutrophils also generate ROS to combat *A. fumigatus* conidia and hyphae (Henriet et al. 2011; Shlezinger and Hohl 2021), e.g., if nicotinamide adenine dinucleotide phosphate hydrogen oxidase is blocked and the ROS generation by neutrophils was disturbed, this could significantly decrease the damage of *A. fumigatus* swollen conidia (Idol et al. 2022). Additionally, *A. fumigatus* has evolved an efficient ROS detoxification system which provides protection in high-ROS environments. Cat1 and Cat2 are known catalase peroxidases; a *cat1* deletion mutant was found to increase conidia susceptibility to hydrogen peroxide in vitro, and delayed infection is observed in rats treated with double *cat1* and *cat2* mutant strains (Paris et al. 2003; Shibuya et al. 2006). A study showed that an *oxrA* deficient strain decreased inflammation, cytokine secretion, and markedly reduced neutrophil influx into the lungs. Furthermore, *cat1* or *cat2* overexpression rescued phenotypes associated with *oxrA* deficiency (Zhai et al. 2021). Additionally, superoxide dismutase enzymes, Sod1 (cytoplasmic Cu/ZnSOD), Sod2 (mitochondrial MnSOD), Sod3 (cytoplasmic MnSOD), and Sod4 are important detoxifying superoxide anions. *Δsod1* and *Δsod2* mutants inhibited hypersensitive growth to menadione, while triple *sod1/sod2/sod3* mutants delayed conidial germination and increased AM sensitivity to killing in immunocompetent mice; however, no significant virulence differences were recorded in immunocompromised murine aspergillosis models when compared with wild-type strains (Lambou et al. 2010). *A. fumigatus* oxidative stress response genes (*ppoA*, *ppoB*, and *ppoC*), non-ribosomal peptide synthetase (*pes1*), and transcription factors controlling responses to external reactive oxidants (*yap1* and *skn7*) have also been reported for the resisting to the host ROS reaction so as to protect the mold from the host defense (Lamarre et al. 2007; Reeves et al. 2006; Schlam et al. 2016; Tsitsigiannis et al. 2005). Furthermore, human and murine neutrophils release neutrophil extracellular traps (NETs), which eliminate extracellular *A. fumigatus*; however, this only decreases polar *A. fumigatus* germ tubes rather than killing the fungi (McCormick et al. 2010). Hence, NET evasion appears to be a strategy permitting pathogen survival and dissemination. Currently, precise *A. fumigatus* evasion mechanisms from NETs are unclear. However, it is reported that degradation of NETs with the DNases, inhibition of NETs release by down-regulating host inflammatory responses, or withstanding the NETs encapsulation are the main escape strategy for respiratory pathogens, including *Bordetella pertussis*, *Haemophilus influenzae*, and group A *Streptococcus* (Storisteanu et al. 2017). In interactions between *A. fumigatus* and neutrophils, interacting hyphae may generate new hyphal branches at de novo tips to avoid neutrophil interactions; therefore, increased branch induction may result in the more aggressive of *A. fumigatus* for the limited number of neutrophils (Ellett et al. 2017).

Monocytes, dendritic cells (DCs), and natural killer (NK) cells are required to control *A. fumigatus* infections. Conidia germination and hyphal growth may be inhibited by monocytes (Schiefermeier-Mach and Haller 2020). Also, NK cells are directly activated against *A. fumigatus* hyphae rather than resting conidia, and if NK cells prestimulated by interleukin (1L)-2, high levels of interferon-γ and granulocyte macrophage colony-stimulating factor were produced, so *A.*

*fumigatus* significantly reduced (Schmidt et al. 2011). NK cells also secrete numerous tumor necrosis factor-α, 1L-18, and galectin-9 molecules to induce macrophage polarization to M1 phenotypes after stimulation by *A. fumigatus* (Zhang et al. 2019). DCs can phagocytose *A. fumigatus* conidia and hyphae to stimulate Th1 cytokine (IL-1A, IL-1B, IL-12B, and TNF-α) and Th2 cytokine production (IL-6 and IL-10) (Bozza et al. 2002; Mezger et al. 2008). When frequent or high fungal burdens occur, acquired immunity is activated. T cells, induced by *A. fumigatus*, protect against invasive aspergillosis (IA) (Hebart et al. 2002). Th2 cells predominate in response to cystic fibrosis (CF) allergic bronchopulmonary aspergillosis (ABPA) patients infected with *A. fumigatus* (Jat et al. 2021). *A. fumigatus* secreted proteins may promote Th2 cell activation (Bozza et al. 2009). Currently, there was still little knowledge about immune evasion for *A. fumigatus*, just to know that after phagocytosis, *A. fumigatus* conidia rapidly escaped from DCs. And NK cell failed to release full granule, NK cell surface activatory receptors NKG2D and NKp46 were contact-dependent down-regulation (Santiago et al. 2018). Thus, more research is required to identify *A. fumigatus* escape strategies from host immune defense systems.

Forming special structures which resist host defenses is a common strategy in pathogenic fungi. Biofilms or aspergilloma are major mechanisms which inhibit host defenses and usually contain numerous hyphae and extracellular matrix (ECM) components which contain virulent factors, including β-D-glucan, galactomannan, and other proteins. Virulence factor release activates immune responses, causes mucus plugging, and eosinophilic pneumonia by generating intense inflammatory reactions (Agarwal et al. 2020). If the lungs are damaged via chronic inflammatory and fibrotic processes, *A. fumigatus* mycelia can successfully grow in abnormal lung mucus, which increases fungal colonization, stimulates Th2-based responses, and favors ABPA development (Kraemer et al. 2006). Fungal biofilms and aspergilloma have significant roles in antifungal resistance (Borghi et al. 2016; Kashyap et al. 2023), while the ECM adsorbs antifungal drugs and prevents their diffusion (Wei et al. 2022). Therefore, fungal cells cannot contact the high concentrations of drugs so they can survive (Wuyts et al. 2018).

Typically, *A. fumigatus* invasion and host defenses are dynamic and complex processes. The host immune system recognizes distinct *A. fumigatus* morphological forms to control growth and prevent tissue invasion, whereas fungi require nutrients and must adapt to hostile environments by escaping immune recognition and counteracting host responses. Understanding these highly dynamic interactions is essential to fully understand aspergillosis pathogenesis and facilitate new therapeutic drug design to overcome morbidity and mortality caused by *A. fumigatus* (Schweer et al. 2014).

## Microecological relationships between symbiotic microorganisms in the lung

As the lungs are an open, interconnective environmental system, *A. fumigatus* and complex microbial mixtures contribute to dynamic microecological homeostasis and are undoubtedly reciprocal in nature (Liu et al. 2021). If a mixed infection, rather than a single infection, occurs, tissue inflammation and damage may be more serious (Neupane et al. 2020). Polymicrobial biofilms are simultaneously formed in the lung, increase antifungal resistance, and are difficult to eradicate using therapeutics (Wang et al. 2020).

## Viruses

*Aspergillus* and viruses are common pathogens, and their inter-microbial interactions occur naturally in clinical settings. Viruses damaging the immune system and infecting the respiratory tract are commonly reported in co-infections with *Aspergillus*. COVID-19 is a novel virus and induces severe acute respiratory syndrome. *A. fumigatus* co-infection rates with COVID-19 in intensive care unit patients in the UK, Netherlands, Germany, Italy, and France were 14.1%, 19.4%, 26.0%, 27.7%, and 33.3%, respectively (Arastehfar et al. 2021; White et al. 2021). When treating COVID-19, the long-term and continual administration of high corticosteroid doses probably limited phosphoinositide 3-kinase/Akt signaling, which upregulated proinflammatory cytokines and promoted FleA signaling activation, thereby facilitating *Aspergillus* spore entry into cells (Banerjee et al. 2021; Steenwyk et al. 2021). Moreover, epithelial lung damage stemming from COVID-19 immunopathology may have facilitated *Aspergillus* superinfections (Marr et al. 2021). Additionally, post-respiratory viral Th-2 immune responses, mediated by increased IL-10 levels, followed by temporary Th1 immune depression and down-regulated macrophage responses, may have facilitated aspergillosis invasion (Lai and Yu 2021; Tavakoli et al. 2020). However, no significant differences were identified between COVID-19 patients and healthy controls in terms of immune response (Moser et al. 2021).

HIV (human immunodeficiency virus) may cause abnormalities that affect immune system components. IA often occurs in advanced AIDS (acquired immune deficiency syndrome) conditions and mainly affects the respiratory tract (Singh et al. 1991). In the lung, radiological data have shown vascular invasion, pulmonary abscesses, bilateral

nodular infiltrates, and cavitary lesions in the upper lobes (Hakkouni and Mansouri 2018). Also, chronic *A. fumigatus* colonization in CF is accompanied by CXCR4 (HIV coreceptor) accumulation in airway granulocytes (Carevic et al. 2015). The *A. fumigatus* Asp f1 protein possesses an amino acid domain that resembles the HIV-1 gp41 heptad repeat 2 (Becker 2007). Additionally, influenza is a common respiratory virus, and mice post-influenza PR/8/34 H1N1 and challenged with *A. fumigatus* had increased fungal and viral burdens, inflammation, and mortality rates. The influenza A-induced signal transducer and activator of transcription 1 molecule inhibited neutrophil recruitment and increased susceptibility to post-influenza IPA (Tobin and Nickolich 2020). Moreover, some viruses occur in co-infections, including *Cetacean morbillivirus*, parainfluenza virus type 3, cytomegalovirus, and respiratory syncytial virus (Cassle et al. 2016; Hassantoufighi et al. 2007; Lee et al. 2010), and which are summarized in Table 2.

## Bacteria

Concomitant colonization by *A. fumigatus* and bacteria is reportedly widespread in immunocompromised or respiratory disease patients. Co-infection pathogens usually exert synergistic effects and mutual interference which depend on airway microenvironmental factors. Interactions between *A. fumigatus* and *Pseudomonas aeruginosa* represent major fungal-bacterial co-operation between pulmonary microbiota (Ostapska et al. 2022). High levels of pyochelin (*P. aeruginosa* metabolite) can transfer iron to the fungal siderophore triacetylfusarinine C for fungal growth (Briard et al. 2019). Pyochelin and phenazines may also kill *A. fumigatus* by inducing oxidative and nitrosative stress and iron starvation; however, sub-inhibitory phenazine, pyocyanin, phenazine-1-carboxamide, and phenazine-1-carboxylic acid concentrations can stimulate fungal growth via iron acquisition (Briard et al. 2015, 2019). When iron levels are high, 2-heptyl-3-hydroxy-4-quinolone enhances fungal metabolism and growth. Furthermore, volatile metabolic by-products containing sulfur groups and released by *P. aeruginosa* benefit fungal growth via interactions with hyphal cell walls (Briard et al. 2016). *A. fumigatus* and *P. aeruginosa* biofilms share a similar chemical composition such that both organisms can generate partially cationic de-N-acetylated exopolysaccharides which are important in biofilm formation. Similarly, cationic exopolysaccharide Pel-containing bacterial culture supernatants may augment *A. fumigatus* biofilm adherence. Similarly, *P. aeruginosa* adhered to *A. fumigatus* hyphae in a cationic exopolysaccharide galactosaminogalactan (GAG)-dependent manner on GAG-coated *A. fumigatus* biofilm coverslips (Ostapska et al. 2022). *P. aeruginosa* also possesses multiple mechanisms that attenuate NET production and resist NET-mediated killing (Block and Zarbock 2021). Further analyses of *P. aeruginosa* strains, isolated from CF patients at early and late disease stages, showed that resistance to NET-mediated killing evolved over time. Thus, *A. fumigatus* and *P. aeruginosa* co-operation is favorable for fungal evasion. Nevertheless, competition between *P. aeruginosa* and *A. fumigatus* has also been reported. Indeed, *P. aeruginosa* was shown to generate siderophore pyoverdine to induce iron starvation and inhibit *A. fumigatus* biofilm metabolism; however, *A. fumigatus* may be self-protected by siderophore production (Sass et al. 2019). In CF, invasive aspergillosis, or chronic obstructive pulmonary disease patients, *A. fumigatus* co-localization with other pathogens (*Streptococcus pneumonia*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Mycobacterium tuberculosis*, and *Mycoplasma pneumoniae*) has been reported (Iwahashi et al. 2020; Moodley et al. 2014; Nogueira et al. 2019; Peccini et al. 2019; Ramírez Granillo et al. 2015). Most of these pathogens also produce biofilms, and inhibitory interactions have been reported depending on the residing microenvironment. *S. pneumoniae* and *S. aureus* are known to disrupt preformed *A. fumigatus* biofilms. Scanning electron microscopy data have shown that *A. fumigatus* mycelial networks are fragmented, hypha are markedly reduced, and short and thin abortive hyphae are formed. Moreover, conidia are scarce, and their surfaces and presented lyses have modified, and finally preformed fungal biofilm ECM had disappeared (Iwahashi et al. 2020; Ramírez Granillo et al. 2015). *K. pneumoniae* renders *A. fumigatus* sensitive to cell wall stress and upregulates cell wall-related genes (Nogueira et al. 2019). Overall, interactions between pulmonary microbiota are complicated, and more studies are required to explore this phenomenon. Other important pathogens are outlined (Table 2).

Currently, there is limited information on the relationships between *A. fumigatus* and other fungi or parasites in the lung. Mixed *A. fumigatus* and *Candida albicans* infections have been identified from the histopathological examination of patient's lungs (Nasri and Fakhim 2019). A combined infection with *A. fumigatus* and the parasite *Pneumocystis carinii* was also found in a disease case, but no further information about their coinfection (Lee et al. 2010). Detailed *A. fumigatus* co-infections with other pathogens are described (Table 2). Future studies are required to examine co-operative interactions between *A. fumigatus* and microbes and show how their interactions facilitate escape from host immune systems in in vitro and in vivo models.

## Drug therapy resistance

In immunodeficient or immunocompromised individuals, opportunistic fungal pathogen infections are now primary factors associated with mortality (Jenks et al. 2020). Therefore, new drug therapies must be explored to treat these pathogens. Currently, echinocandins, azoles, and polyenes

**Table 2** Examples of pathogen co-infection with *Aspergillus fumigatus*

| Organism | The relationship with *A. fumigatus* | Reaction mode | Reference |
|---|---|---|---|
| Cetacean morbillivirus | Co-infection | They were co-detection in lung and identified pneumonia at autopsy | (Cassle et al. 2016) |
| Parainfluenza virus type 3 | Co-infection | It can be co-infected with cytomegalovirus, *A. fumigatus* and *P. carinii* to caused severe pneumonia | (Lee et al. 2010) |
| Respiratory syncytial virus | Promote infection | The co-infection of them showed the exacerbation of the inflammatory response and increased airway responsiveness to methacholine | (Hassantoufighi et al. 2007) |
| Pneumonia virus | Co-infection | The co-infection of them showed the asthmatic inflammatory response for mice | (Percopo et al. 2014) |
| Human cytomegalovirus | Mix infection | It can be mixed infection with pathogens including *A. fumigatus*, *Nocardia nova*, and *Mycobacterium tuberculosis* in pulmonary | (Yan et al. 2022) |
| Human immunodeficiency virus | *A. fumigatus* infection is occurring after HIV infection | The mix infection of them could cause respiratory tract, vascular invasion, pulmonary abscesses, bilateral nodular infiltrates, and cavitary lesions in the upper lobes | (Singh 2021) |
| COVID-19 | Co-infection | The patients with COVID-19 could be infected with *A. fumigatus* to caused IPA | (Lai and Yu 2021) |
| Influenza H1N1 virus | Co-infection | The patients challenged with influenza could subsequently challenge with *A. fumigatus* to cause postinfluenza invasive pulmonary aspergillosis | (Tobin and Nickolich 2020) |
| *Mycobacterium abscessus* | Co-infection | The mix infection of them could increase the lung inflammation and decreased mycobacterial burden in mice | (Monin et al. 2018) |
| *Pseudomonas aeruginosa* | Synergistic effects | *P. aeruginosa* could stimulate the growth and biofilm formation of *A. fumigatus* | (Briard et al. 2016; Ostapska et al. 2022) |
| *Streptococcus pneumoniae* | Competition effects | *S. pneumoniae* could suppressed the development of *A. fumigatus* biofilm and disrupted the preformed *A. fumigatus* biofilm | (Iwahashi et al. 2020) |
| *Staphylococcus aureus* | Competition effects | *S. aureus* could inhibit the development of biofilm formed by *A. fumigatus* | (Ramírez Granillo et al. 2015) |
| *Klebsiella pneumonia* | Competition effects | The spore germination, hyphal development and biofilm formation of *Aspergillus* species could be inhibited at the presence of *K. pneumonia* | (Nogueira et al. 2019) |
| *Mycobacterium tuberculosis* | Synergistic effects | Aspergilloma formed by *A. fumigatus* is usually located in the cavity of old tuberculosis | (Moodley et al. 2014) |
| *Mycoplasma pneumoniae* | Co-infection | *M. pneumoniae* was coinfected with *A. fumigatus* to cause ABPA | (Peccini et al. 2019) |
| *Stenotropho monas maltophilia* | Co-infection | The concomitant lung colonization of *A. fumigatus* and *S. maltophilia* was mainly in patients with cystic fibrosis | (Cabaret et al. 2016) |

**Table 2** (continued)

| Organism | The relationship with *A. fumigatus* | Reaction mode | Reference |
|---|---|---|---|
| *Nocardia nova* | Mix infection | Mixed pulmonary infection with pathogens including *Nocardia nova*, *M. tuberculosis*, *A. fumigatus*, and human cytomegalovirus | (Yan et al. 2022) |
| *Candida albicans* | Co-infection | The mixed *C. albicans* and *A. fumigatus* lung infection in the patient on prolonged steroid therapy | (Chen et al. 2021) |
| *Pneumocystis jiroveci* | Co-infection | The mixed infection of *P. jiroveci* and *A. fumigatus* could cause lung inflammation | (Vipparti 2014) |

are the main conventional therapies used to clinically treat *A. fumigatus*. In contrast, and thanks to widespread clinical-drug use, fungi have evolved several escape mechanisms to withstand antifungal drug damage. For example, *Candida auris* is a multidrug-resistant fungus and resistant to almost all antifungal agents (Chowdhary et al. 2020).

## Antifungal drug use against *A. fumigatus* in clinical settings

The fungal cell wall provides structural integrity, protection, and physical defenses against adverse environments. More importantly, cell wall is absent in human cells and has been successively targeted using innovative drug design (Zhou et al. 2022). β-1,3-D-glucan synthase is encoded by *fks1,* is required for cell wall assembly, and has been used as a target for antifungal agents for antifungal agent echinocandins (Satish et al. 2019), Caspofungin, anidulafungin, and micafungin are the representatives of this group (Revie et al. 2018). Caspofungin is fungistatic against *A. fumigatus* and reduces the increase growth of mold by caspofungin paradoxical effect (CPE) means. The proteins involved in CPE responses contain the basal modulation of the RNA polymerase II initiation sites, calcium metabolism, and cell wall remodeling (Mattos et al. 2020; Valero et al. 2020). Micafungin is an effective prophylactic antifungal agent and has been used in patients with hematological diseases (e.g., acute leukemia) who are at high risk of invasive mold infections (Park et al. 2019; Siopi et al. 2021). The drug significantly up-regulates the conidiophore *brlA* gene and alters *Aspergillus nidulans* morphology (Reese et al. 2021). Importantly, antifungal prophylaxis success rates are up to 80% in hematopoietic stem cell transplant recipients when administered micafungin (50 mg/day) (Jarvis et al. 2004). Additionally, anidulafungin therapy increases survival and improves pulmonary infarct scores for pulmonary or disseminated aspergillosis in animal models (Pfaller 2004).

The cell membrane is also an important drug target for protecting the cell interior. Specifically, ergosterol is the most important membrane sterol in fungal cells, but is not found in human cell membranes. Two agents related to ergosterol are widely used in clinical practice: azoles and amphotericin B (AMB) (representative polyene agent). Azoles have excellent antifungal activity and are the only oral drugs with anti-*Aspergillus* activity. Azoles inhibit the cytochrome P450-dependent enzyme 14α demethylase (Cyp51) to block the channel of lanosterol conversion into ergosterol (Emami et al. 2017). *A. fumigatus* demonstrated intrinsic resistance to fluconazole, while the triazole antifungals itraconazole, voriconazole, isavuconazole, and posaconazole are favored treatment options against aspergillosis. In an immunosuppressed IPA rabbit model, 40 mg/kg itraconazole had in vivo antifungal activity; however, near-peak itraconazole plasma concentrations varied from 0.5 to 16.8 μg/mL. And the antifungal activity in an inhibitory sigmoid maximum-effect model was strongly correlated with itraconazole plasma concentrations (Berenguer et al. 1994). Previous studies also reported that itraconazole effectively treated ABPA by decreasing immunological severity (Pasqualotto et al. 2009). Voriconazole and posaconazole are effective therapies for asthma in ABPA and severe asthma (Agarwal 2012). AMB binds to sterols in lipid bilayers to form large, extra-membranous aggregates which cause membrane leakage and fungal death (Agarwal 2012). When treated with 0.5 mg/mL AMB, approximately 90% of *A. fumigatus* protoplast permeability was lost and fungal death ensued (Mousavi and Robson 2004). In clinical settings, AMB administration exhibited dose-limiting toxicity, nephrotoxicity, and infusion-related reactions; therefore, several AMB formulations have been generated: amphotericin B deoxycholate (DAMB), liposomal amphotericin B (LAmB), AmpB lipid complex, and AmpB colloid dispersions (Monk and Goffeau 2008). In 2008, Infectious Diseases Society of America aspergillosis guidelines recommended that LAmB could be used for patients with IA, where voriconazole was not appropriate; thus, a 3 mg/kg/

day LAmB dose was advocated (Lanternier and Lortholary 2008). Moreover, monocytes, exposed to a combination of *A. fumigatus* and DAMB, expressed decreased cytokine (IL-10, IL-2, and IL-3) and up-regulated IL-1β levels (Simitsopoulou et al. 2011). Furthermore, polyene and azole combinations increased survival and demonstrated a significantly greater reduction in tissue burden when compared with monotherapies (Martin-Vicente et al. 2016).

## Drug resistance in *A. fumigatus*

Azole resistance is the most common phenomenon in *A. fumigatus*. It is reported that patients with chronic pulmonary aspergillosis, when treated with voriconazole, show 5% resistance rates (Bongomin et al. 2018). Also, 11% of itraconazole-treated patients were resistant to *A. fumigatus*, and PCR data identified *A. fumigatus* resistance rates of up to 55%, suggesting that increased azole-resistance burdens were limiting factors in aspergillosis treatment (Bongomin et al. 2018; Singh et al. 2020). Mechanistically, cyp51- and non-cyp51-mediated azole resistance actions are implicated in these phenomena. Underlying cyp51-mediated resistance mechanisms are primarily linked to structural changes or the up-regulated azole target lanosterol 14-α-demethylase, especially the *cyp51A* gene with various of tandem repeat (TR) fragments in the promoter region, causing significant overexpression of the *cyp51A*. The cyp51-mediated resistance mechanisms mainly contain TR integrations alone or combined with amino acid substitution in the coding gene: TR34/L98H, TR34/L98H/S297T/F495I, TR46/Y121F/T289A, TR53, and TR120 (Garcia-Rubio et al. 2017; Snelders et al. 2008). Another important mechanism underpinning azole resistance is efflux pump gene overexpression which increases multidrug resistance, whereas deletion shows multidrug sensitivity (Meneau et al. 2016). Currently, approximately 49 putative ATP-binding cassette transporters and 278 major facilitator superfamily members have been identified in *A. fumigatus* genomic sequences. Efflux pumps genes, including *abcD*, *abcE*, *atrB*, *atrC*, *atrF*, *atrI*, *cdr1B*, *mdr1*, *mdr2*, *mdr3*, and *mdr4*, are related to azole resistance (Pérez-Cantero et al. 2020; Rivero-Menendez and Alastruey-Izquierdo 2016). Additionally, cell membrane homeostasis, calcium signaling, cell wall integrity, Hsp90-calcineurin pathway, HOG-MAPK signaling, and iron balance are reportedly involved in azole stress responses (Chen et al. 2020).

AMB has broad activity against pathogenic fungi and is associated with lower antifungal resistance rates. AMB-resistant *Aspergillus* spp. are related to cell wall composition rather than ergosterol content and possess α-1,3-glucan and protein complex alterations in the outermost wall layer

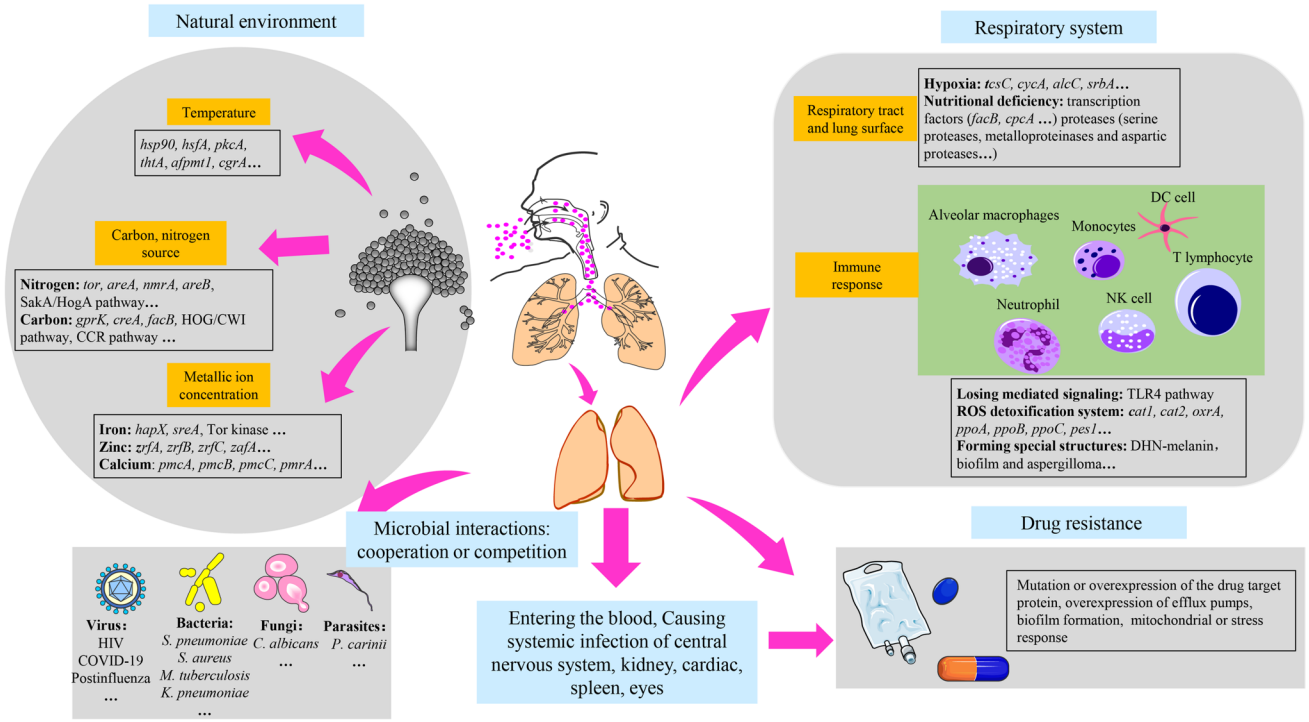


**Fig. 1** The negative threats encountered by *A. fumigatus* and putative molecules/pathways required for fungal escape. The orange boxes represent the negative threats encountered by *A. fumigatus*, and the putative molecules/pathways required for fungal escape have been demonstrated in rectangle box text in gray area

(Seo et al. 1999). However, protoplasts and conidia in AMB-resistant *A. terreus* have no impact on cell walls (Posch et al. 2018). Currently, echinocandin resistance mechanisms in *Aspergillus* remain under-characterized. For *A. fumigatus*, the target of echinocandin, glucan synthetase encoding gene *fks1* site-directed mutation increased 16-fold resistance to caspofungin. Interestingly, the spontaneous mutants digested cell wall were sensitive to low levels of drug but displayed nearly normal growth above 0.5 μg/ml, and those mutations without significant differences in the chitin and β-1,3-glucan distributions for the mutant and wild-type strains (Gardiner et al. 2005). Together, target gene mutations or alterations in cell wall components are important reasons for the emergence of increased drug resistance to *Aspergillus*.

## Conclusions

In summary, *A. fumigatus* escape strategies from adverse living conditions are varied and complex. To survive natural environmental factors, including temperature and nutritional stress, and after entering the host for the growing challenge from the immune response, *A. fumigatus* has evolved several signal receptors, transmitters, effectors, and mutant target proteins to respond to these pressures. Moreover, *A. fumigatus* hyphae can penetrate lung epithelial tissue, invade blood vessels, and spread through the circulation to other organs (Latgé and Chamilos 2019). Although several therapies have been developed to treat this mold, new drugs are required against drug-resistant strains (Zhang et al. 2021b).

Apart from *A. fumigatus*, other *Aspergillus* species, including *A. flavus*, *A. terreus*, and *A. niger*, are common mold infections in humans and cause several serious diseases in both immunocompetent and immunocompromised patients (Stemler et al. 2023). Thus, are there differences between other *Aspergillus* spp. infections *and A. fumigatus* processes? How about the negative threats that other *Aspergillus* spp. encountered in the natural environment and the immune response in host? To answer these questions, future research on fungal epidemiology or secondary infections caused by *Aspergillus*, especially *A. fumigatus*, are required (Fig. 1).

Identifying more effective antifungal drug targets and drug repurposing strategies is required to combat *A. fumigatus* infections. However, antifungal studies have only focused on in vitro outcomes. More in vivo animal model and clinical studies are required to evaluate antifungal effectiveness in vivo (Zhou et al. 2023).

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**Data Availability** Data sharing is not applicable to this review article as no new data were created in this review article.

## Declarations

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Conflict of interest** The authors declare no competing interests.

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