Iron Assimilation

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Iron is a key transition metal required by most microorganisms and is prominently utilised in the transfer of electrons during metabolic reactions. The acquisition of iron is essential and becomes a crucial pathogenic event for opportunistic fungi. Iron is not readily available in the natural environment as it exists in its insoluble ferric form, i.e., in oxides and hydroxides. During infection, the host iron is bound to proteins such as transferrin, ferritin, and haemoglobin. As such, access to iron is one of the major hurdles that fungal pathogens must overcome in an immunocompromised host. Thus, these opportunistic fungi utilise three major iron acquisition systems to overcome this limiting factor for growth and proliferation. (Draft for definition)

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1. Introduction

In biology, iron is an essential micronutrient for almost all eukaryotes and most prokaryotes[1] . Iron is the fourth most abundant trace element in the environment, but the bioavailability (Fe^{2+}) is limited due to oxidation into the insoluble ferric hydroxides (Fe^{3+}) by atmospheric oxygen[2] [2]. In this state, iron has a solubility of approximately 10^{-9} M at neutral pH[3] [3]. Nonetheless, the involvement of iron in numerous important metabolic processes and as enzyme cofactors is due to its capacity for electron exchange[4] [4]. This transition metal is required in DNA, RNA and amino acid synthesis, oxygen transport, cellular respiration (iron-sulphur cluster (Fe-S) containing ferredoxins, haem-containing cytochromes), enzymatic reactions such as Fe-S proteins, e.g., fumarase and aconitase of the tricarboxylic acid cycle (TCA cycle)[5][6][7] [5–7]. Although it is a key trace element, iron also presents a danger to biological systems. Iron (Fe^{2+}) triggered Fenton reaction produces reactive oxygen species (ROS) such as superoxide ($O_2•^-$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH•) (Equation 1)[8] [8]. Hydroxyl radicals produced during these reactions are deleterious and can damage cellular components such as DNA, proteins, and lipids[9] [9]. Due to the redox property of iron, it is imperative that organisms have tightly regulated homeostatic mechanisms to maintain enough intracellular iron while actively avoiding the detrimental effects of excess iron[10] [10].

Fe^{3} + $O_2•$ à Fe^{2} + O_2

Fe^{2+} + H_2O_2 à Fe^{3+} + OH• + OH^-

Net Reaction: $O_2•^-$ + H_2O_2 à OH• + OH^- + O_2

In low iron environments, cells employ strict iron usage called the iron-sparing response, which allows small concentrations to be used in essential enzymatic processes[11] [11]. High-affinity acquisition systems are expressed under these conditions, which allows for the rapid and efficient uptake of iron [12][3,12]. Under high-iron conditions, these uptake systems are repressed, and excess iron is stored in intracellular compartments, e.g., vacuole or ferritin in mucoralean fungi[3][13][14] [3,13–15]. [15]

In the host, iron is kept extremely low (i.e., < 10^{-24} M for Fe^{3+} in serum), and other trace metals, are usually bound to proteins[16] [16]. During infection, iron is further restricted by numerous host mechanisms[17] [17]. These mechanisms function by actively chelating extracellular Fe^{3+} to high-affinity iron-binding proteins such as glycoproteins, transferrin, and lactoferrin, including intracellular sequestration by haemoglobin, ferritin, cytochromes, and the hepcidin axis, to name a few[2][18] [2,18]. These elegant pathways and mechanisms for controlling systemic iron concentrations are known as nutritional immunity, and its importance in the host immune response to infections has been thoroughly described[2][17][19] [2,17,19]. [19][20]

Invading fungal pathogens must overcome these limitations to access host iron and other key metals such as zinc, copper, manganese, and nickel to proliferate and cause disease. As such, healthy individuals are usually not susceptible as their immune system is robust[17] [17]. On the other hand, fungal pathogens can cause debilitating and devasting diseases to various patient groups, especially among those who are immunocompromised or hospitalised with severe underlying conditions[20][21] [20,21]. Those at high risk include patients undergoing haematopoietic stem cell (HSCT), solid organ transplant recipients (SOTs), AIDS patients, those receiving antilymphocyte monoclonal antibodies, and other immunomodulators, as well as patients with other underlying diseases associated with immune dysfunction[20][21] [20,21]. Opportunistic fungal infections are underappreciated in comparison to bacterial, viral, and parasitic infections[22] [22]. With the current advancements in medicine and the increasing cohort of immunosuppressed individuals, the mortality rate caused by fungal infections is on a constant rise[23] [23]. For instance, *Candida albicans* and other *Candida* species are the most common fungal pathogens responsible for superficial mucosal infections as well as life-threatening systemic diseases[24] [24]. *Cryptococcus neoformans* is the most important opportunistic pathogen in HIV/AIDS patients. Although access to antiretroviral therapy (ART) has improved globally, the number of cryptococcal infections remains high, with an estimated 278,000 reported cases worldwide and a mortality rate of approximately 81%[24][25][26][27][28] [24–28]. *Aspergillus fumigatus* and other pathogenic *Aspergillus* species cause a wide spectrum of diseases known as aspergilloses. These include allergic bronchopulmonary, chronic pulmonary, and invasive aspergillosis[29] [29]. As fungi cause serious opportunistic infections, there is a new precedent for novel approaches in treatment options, as the range remains limited and there are increasing reports of resistance[30] [30].

2. The Reductive System for Iron Uptake

The mechanism for iron acquisition and homeostasis has been well documented in the model organism *Saccharomyces cerevisiae*, which established the foundations for further studies in fungal pathogens[31] [34]. There are two main mechanisms for iron uptake in *S. cerevisiae*, the reductive high affinity (HA) and non-reductive systems[32][33] [35,36]. The reductive HA pathway involves three sequential steps: (i) the initial reduction of ferric (Fe^{3+}) to ferrous (Fe^{2+}) iron by a dedicated membrane-bound ferric reductase encoded by *FRE1* and *FRE2* genes; (ii) the re-oxidation to ferric iron (Fe^{3+}) by the multicopper ferroxidase (ferroxidase) encoded by the *FET3* gene; and (iii) the import of the insoluble ferric iron (Fe^{3+}) by the high-affinity iron permease encoded by the *FTR1* gene[34][35][36] [37–39] (Figure 1). The non-reductive system involves the use of siderophores (xenosiderophores) that bind iron, which are then translocated across the membrane via specific/specialised transporters. This will be discussed later [34][37][38][37,40,41].

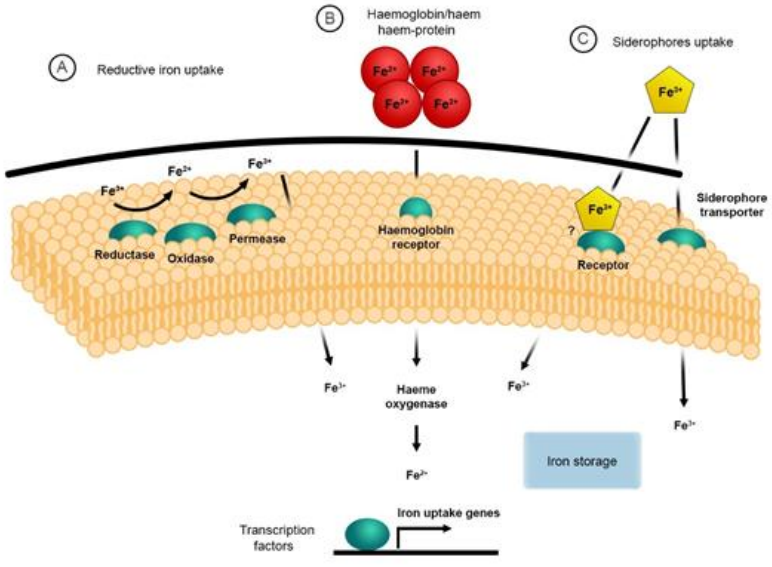

Figure 1. General strategies for iron acquisition in pathogenic fungi. (**A**) the reductive system responsible for iron assimilation via reduction and oxidation followed by transport into the cytoplasm via specialised iron permeases; (**B**) haem -iron uptake and degradation, which facilitates iron chelation from haemoglobin and haem -proteins; (**C**) siderophore uptake system that allows for iron acquisition from a spectrum of siderophores and xenosiderophores (figure adapted from [40]).

Fungal pathogens such as *C. neoformans*, *C. albicans* and *A. fumigatus* as well as pathogenic Mucorales, i.e., *Rhizopus arrhizus* (syn. *R. oryzae*, *R. delemar*), *Mucor circinelloides* and *Lichtheimia corymbifera* possess a reductive iron uptake system[39] [42]. This system has highly conserved orthologs of the three major components, i.e., surface ferric reductases, ferroxidases and permeases similar to those identified in *S. cerevisiae* [31][32][40][34,35,43]. For these pathogens, the

reductive HA pathway is important for releasing ferric iron bound to other complexes, e.g., transferrin, ferritin, or siderophores[41][42][43][44][45]44–48]. The latter organism, *L. corymbifera*, has recently been shown to have conserved orthologs belonging to this system[46] [49]. It has been demonstrated that the ferric reductases are also involved in intracellular iron transport and storage of iron when present on the vacuole membranes[47][48] [50,51]. The ferric reductases encoded by the *FRE* genes are integral membrane proteins that require NADPH, flavin mononucleotides (FMN), and haem for their activity. The oxidation of cytoplasmic NADPH is catalysed by these ferric reductases, which then transfer the electron across the plasma membrane to facilitate the reduction of metals, e.g., iron[49][50][51] [52–54]. It has also been shown that these reductases have cupric reductase activity, and they can facilitate the use of siderophore-bound iron [32][41][42][49][52][35,44,45,52,55]. Eight putative ferric reductases have been identified in *C. neoformans*; these are *FRE1–FRE*7 and *FRE201*[49] [52]. The transcription of *FRE2* and *FRE4* is regulated by $FeCl_3$ or haemin, which indicates that these genes may have an important role in iron homeostasis during iron-starvation. Saika et al., 2014 demonstrated that Fre2 is essential for fungal growth in the presence of transferrin and haem and contributed to virulence in mouse inhalation model of cryptococcosis[49] [52]. Copper also plays a role in the transcriptional regulation of the *FRE* genes in *C. neoformans*, *C. albicans*, and *S. cerevisiae*[49][50][53][54][55] [52,53,56–58].

As previously mentioned, the next stage in the reductive iron uptake system involves the transport of the reduced iron by the high-affinity ferric transporters. This transport system requires the dual-protein complex consisting of the ferroxidase Fet3 and the permease Ftr1. The ferroxidase, Fet3, catalyses the oxidation of ferrous (Fe^{2+}) to ferric iron (Fe^{3+}), which is immediately transported into the cell by the permease Ftr1[56] [59]. Components of the reductive iron uptake system have been identified and characterised in numerous opportunistic fungal pathogens, most of which are thoroughly summarised in the following review[57] [60]. Characterised and putative homologs of the reductive pathway components have been identified in pathogenic Mucorales and are summarised in Table 1. To date, five genes—*FET3*, *FET31*, *FET33*, *FET34,* and *FET99*—have been identified in *C. albicans* that are orthologs to the *S. cerevisiae FET3* gene[41][58][44,61]. Under iron starvation, it has been shown that both *FET3* and *FET34* and the permease *FTR1* are regulated. *FET34* has an important role in iron acquisition, hyphal growth, and virulence in murine models of systemic candidiasis [59][62]. Ftr1 and the ferric reductase Fre10 may be involved in iron acquisition from host proteins, i.e., ferritin and transferrin [42][60][61] [45,63,64]. Interestingly, virulence in a mouse model of systemic candidiasis is attenuated in *FTR1* knockouts, and this strongly indicates that the permeases are key virulence determinants[3][61] [3,44,45,63].

Table 1. Reductive iron acquisition system in *S. cerevisiae* and pathogenic Mucoralean species.

Component	Species	Gene	Functions	Ref
Ferric reductases	*S. cerevisiae*	*FRE1, FRE2*	Ferric iron reduction at the cell surface	[3][33][62][63] [3,36,65]
	Rhizopus spp	*FRE* (homolog)	Putative protein—ferric iron reduction at the cell surface	[45][64][48,66]
	M. circinelloides	*FRE* (homolog)	Putative protein—ferric iron reduction at the cell surface	[44][65][47,67]
	L. corymbifera	*FRE5* (homolog)–three copies	Putative protein—ferric iron reduction at the cell surface	[46][49]

	S. cerevisiae	*FET3*	Multicopper-oxidase Ferrous iron oxidation and high-affinity uptake coupled with Ftr1 (permease)	[3][66][63] [3,55,65,68]
Multicopper ferroxidase	*Rhizopus* spp	*FET3* homolog	Putative multicopper oxidase	[45][48]
	M. circinelloides	*FETA, FETB, FETC*	Ferrous iron oxidation and high-affinity iron uptake	[44][47]
	L. corymbifera	*FET3/5* homolog–three copies	Putative multicopper oxidase	[46][49]
Iron permease	*S. cerevisiae*	*FTR1*	High-affinity iron uptake, coupled with FET3 (multicopper oxidase)	[3][56][66][63][67] [3,59,68–70]
	Rhizopus spp	*FTR1*	High affinity iron permease	[62][68][69] [65,71,72]
	M. circinelloides	*FTR1* (homolog)	Putative iron permease	[44][70][47,73]
	L. corymbifera	*FTR1* (homolog) *—four copies*	Putative iron permease	[46][49]

The components of the reductive iron uptake system are also present in *A. fumigatus*. These include the cell-surface ferric reductases, ferroxidases (FetC), and the iron permease (FtrA). Like *C. albicans* Ftr1, the *FTRA* gene of *A. fumigatus* is also expressed under iron starvation. Mutants with an inactivated *FTRA* gene showed no difference in growth on iron-depleted medium and in virulence models compared to wild-type *A. fumigatus*, thereby indicating that the permease is not a virulence factor in *A. fumigatus*[71][72] [74,75]. In Mucorales, this system was shown to be strongly regulated, particularly in low iron conditions[44][45] [47,48]. Recently, it was demonstrated that there is overexpression of the ferroxidases (*FET3*) in the lung of mice confronted with invasive *M. circinelloides* [44][47]. In addition, there are three characterised copies of *FET3* (Table 1.) in *M. circinelloides*, which were identified as *FET3A*, *FET3B,* and *FET3C,* with the latter being the most important for infection [47]. Single and double knockout strains of the *FET3* genes were also shown to be critical components involved in iron uptake, particularly in low iron conditions both in vitro and in vivo[44] [47]. In *R. delemar*, the complete deletion of the iron permease (*FTR1*) results in reduced virulence[45][64] [48,66]. Interestingly, iron starvation induces the metacaspase dependent apoptotic response in strains lacking *FTR1*[45] [48]. In addition, there remains the possibility that the reductive pathway and the iron permeases (Ftr1) in Mucorales may also have a role in scavenging iron from other host proteins, e.g., ferritin or transferrin [64][64][40,64,76]. These examples highlight the importance of the reductive pathway has in survival and virulence under iron starvation.

Iron Acquisition and Susceptibility to Antifungals: implications in Therapy

Antifungal Treatment and Iron Chelation Therapy

Successful management of IFIs are based on the timely initiation of optimal antifungal therapy, reversal or discontinuation of underlying predisposing factors and the use of relevant adjunctive therapies[73] [222]. Additionally, immediate correction of metabolic disorders or abnormalities in patients with uncontrolled diabetes is mandatory in suspected mucormycosis cases. Surgical intervention for the complete removal of infected tissue in urgent cases significantly improves patient outcome[74][75][76][77] [199,202,204,223]. Only four classes of antifungal medications are currently available for the treatment of IFIs, these are: polyenes, pyrimidine analogue, echinocandins and triazoles[78][79][80] [207,210,224]. The latter i.e., echinocandins and azoles will be discussed later as emerging resistance is becoming more prevalent [81][225]. The first line treatment of invasive candidiasis is typically the echinocandins as well as formulations of amphotericin B (AMB) [82] [205]. For Cryptococcal infections, the gold standard antifungal drugs include the polyenes, flucytosine (5-FC), triazoles and their combinations [83][84][226,227]. Treatment options for invasive aspergillosis include voriconazole,

liposomal amphotericin B (LAMB) and most recently isavuconazole[74][85][86] [199,228,229]. In mucormycosis, the lipid formulations of AMB, i.e., LAMB and AMB lipid complex, (AMLC) is the optimal treatment option[74][75][76][73][85][87][85] [199,202,204,222,228,230]. It is important to note that Mucoralean fungi are innately resistant to most antifungals in vitro, including voriconazole[88] [231]. Most recently, posaconazole and isavuconazole have exhibited activity against Mucorales [85][88][89][228,231,232]

Currently, therapeutic strategies to combat complicated infections as well as innate, emerging resistance in fungal pathogens include adjunctive therapies and new antifungal drugs[90] [233]. Adjunctive therapies functions by interfering with resistance mechanisms or modifying drug activity[91] [197]. Examples of the former include efflux pump inhibitors, which increase intracellular antifungal concentration, and histone deacetylase inhibitors, which are used in combination with azoles to inhibit fungal growth[91][92][93][94] [197,234–236]. Compounds that modify antifungal activity usually act synergistically by altering the fungal stress response mechanisms[95][96][97][98] [237–240]. These include statins, heat-shock protein 90 (Hsp90) inhibitors, nonsteroidal anti-inflammatory drugs, inhibitors of calcineurin and calmodulin, calcium homeostasis, selective serotonin reuptake, and iron homeostasis[91][78] [197,207].

Iron metabolism holds a central role in fungal pathogenesis, particularly in the development of mucormycosis. Thus, there is the possibility to use iron chelators as an adjunctive therapy strategy as this could limit/inhibit fungal growth. The iron chelator deferasirox is used for the treatment of iron overload in immunocompromised patients and those with elevated serum iron, e.g., diabetic & DKA patients. Preclinical data on DKA murine models of *R. oryzae (R. arrhizus)* infection found that treatment with deferasirox was as effective as LAMB therapy and combination treatment, i.e., deferasirox-LAMB, acted synergistically to improve survival[99][100][101][102][103] [31,101,143,241,242]. Although this showed promise, in the clinical application of deferasirox-LAMB, it was demonstrated to significantly increase mortality in patients with hematologic malignancies[100] [101,210,241,243,244]. On the other hand, this treatment strategy remains a viable option for other high-risk patient groups, e.g., DKA patients [200,202]. Deferasirox was also seen to enhance LAMP treatment in a murine model of invasive pulmonary aspergillosis. However, relevant clinical applications or data remain lacking [242,245]. Synergy was shown with fluconazole, ketoconazole, or AMB when combined with other iron chelators, including deferiprone, lactoferrin, and ciclopirox. These combinations proved successful in inhibiting *A. fumigatus* growth in vitro [237]. Another potential novel target for the treatment of Mucorales include the inhibition or blocking of the proteins involved in the reductive pathway. Antibodies targeting the iron permeases (Ftr1) of *R. oryzae (R. arrhizus)* protected DKA mice from infection [33,72,246]. Additionally, antibodies targeting the unique host proteins involved in receptor mediated endocytosis of fungal spores, i.e., 78kDa glucose-regulated protein (Grp78/HspA5) are possible targets. Grp78/HspA5 is overexpressed in patients with hyperglycaemia, DKA, and elevated serum iron; thus, antibodies, i.e. anti-Grp78 may be promising novel targets as it was shown to offer protection in a murine DKA model. Similar protective attributes were seen when antibodies of the fungal spore coat protein H or CotH i.e., anti-CotH (the interaction partner of Grp78/HspA5) were used in DKA murine model [105,231,247].

Antifungal Resistance and Iron

Echinocandins

Antifungal compounds that specifically target the cell wall components include Ibrexafungerp (SCY-078) and the Echinocandins, e.g., caspofungin, micafungin, and anidulafungin [181,248]. Ibrexafungerp (SCY-078) functions by actively inhibiting the 1,3-β-D-glucan synthase while the Echinocandins inhibit the 1,3-β-D-glucan synthase by noncompetitively binding to the Fksp subunit of the enzyme, which leads to a decrease in the amount of β-D-glucans present in the cell wall (Figure 5.) [249–254]. Cell death is seen in *C. albicans* when this enzyme is inhibited by caspofungin and micafungin [252,254–257]. Interestingly, Δ*CCC2* cells (defectives in copper transport) show hypersensitivity to echinocandins [258]. On the other hand, elevated proportions of chitin in the cell wall of *Candida* species exhibit increased resistance to caspofungin, particularly in in vivo candidiasis models [238,248,251,259]. Recently, Pradhan et al. 2019 demonstrated that iron-limitations induces a β-glucan masking phenotype as well as cell wall remodelling and thickening. However, defects in this phenotype was observed in mutants lacking the permease and transcription factor (Δ*FTR1* and Δ*SEF1,* respectively) [64]. Through this β-glucan masking, there is reduced phagocytosis and a dramatic reduction in proinflammatory cytokines (TNF-α and IL-6) produced by peripheral blood mononuclear cells (PBMCs) [64,163,164]. However, the use of caspofungin enhances β-glucan exposure [163,164]. Interestingly, the 1-3-β-d-Glucan inhibitor ibrexafungerp appears to be effective against clinical isolates that are resistant to echinocandins [260,261]. The dynamic nature of the cell wall has a major role in the development of antifungal resistance [262,263]. In both *C. albicans* and *A. fumigatus*, changes in the structural composition of the cell wall have been noted in strains showing antifungal resistance [210,213,214].

Azoles

Azole antifungals have been in clinical use for more than 20 years [264]. The azoles are separated into two distinctive classes, i.e., the triazoles and the imidazoles. Triazoles used in the clinical setting include fluconazole, itraconazole, voriconazole and posaconazole [265]. Common imidazoles used are clotrimazole, ketoconazole and miconazole [265,266]. Cytochrome P450 (CYP450) is an enzyme that converts lanosterol to ergosterol, which is the major sterol in the fungal plasma membrane. Azoles inhibit the CYP450 enzymes which causes increase permeability of the fungal plasma membrane (Figure 5.) [265–267]. Azoles also affect other efflux transporters, including major facilitator superfamily (MFS) transporters and ATP-binding cassette (ABC) transporters [268]. Susceptibility to azole antifungals is seen in *Candida* spp, *C. neoformans*, *Aspergillus* spp, and the Mucorales, to name a few. However, resistance has also been well characterised among this class of antifungal therapy [239,268–271]. The direct target of fluconazole is Erg11 (homologous to the yeast CYP51 F5), an enzyme involved in the ergosterol biosynthesis pathway [97,240,272,273].

In *C. albicans*, it was shown that intracellular iron depletion leads to increased fluidity of the plasma membrane as there is reduced ergosterol [240,274]. Gene expression of *ERG11*, which encodes for lanosterol 14-α demethylase as well as the *ERG3* gene, which encodes for the Δ5,6-desaturase is affected by intracellular iron availability (Figure 5.). Erg3 catalyses the addition of a carbon-carbon double bond to the substrate molecules in the finals steps of the ergosterol biosynthesis pathway [39,240,271,275]. The strains lacking the high-affinity iron permease Ftr1 (Δ*FTR1*), null mutants (lacking both: Δ*FTR1* and Δ*FTR2*) as well as *ΔCCC2* mutants (copper transporter) were all shown to be more susceptible to fluconazole [240]. An important note is that the Ccc2 copper transporter is responsible for the copper acquisition, as copper is a key component of the multicopper oxidase (Fet3) protein in the reductive pathway [240,258]. Iron deprivation results in the downregulation of *ERG11* [240,271]. As such, the increased membrane fluidity due to lower ergosterol content seen in the iron uptake mutants (Δ*FTR1*, Δ*FTR2*, Δ*FTR1* Δ*FTR2*, and *ΔCCC2*) leads to higher passive diffusion of azole antifungals, thus increased susceptibility [271,276]. This is compounded by the upregulation of *ERG3*, which in an azole-inhibited pathway, allows for the accumulation of toxic intermediates [39,271]. Therefore, Erg3 acts synergistically with azoles increasing susceptibility [239,240,271]. On the other hand, mutations or deletions of the *ERG3* gene, as well as upregulation of *ERG11,* confers azole resistance in *C. albicans* (Figure 5.) [271,275,277]. Similarly, the reductive iron uptake system in *C. neoformans* has an important role in resistance to azoles [97,138,278]. Mutants lacking both the multicopper ferroxidase (*CFO1*) and the iron permease (*CFT1*) had reduced intracellular iron levels, which significantly increase azole drug susceptibility, i.e., to fluconazole [97,279]. Interestingly, overexpression of *ERG11* in *CFO1* mutants exhibited reduced susceptibility to fluconazole [97,272,277,280]. Innate and acquired reduced susceptibility and resistance to azole in *A. fumigatus* has been linked to numerous point mutations in the *CYP51A* gene [268,270,281]. It has been demonstrated that the Mucorales have an intrinsic resistance to azole antifungals, specifically to the short-tailed azoles, i.e., fluconazole and voriconazole [270,281–284]. It was found that this intrinsic resistance may be caused by an amino acid substitution in the cytochrome P51 or CYP51 F5 (Erg11) enzyme; changing a Tryosine (Y) to Phenylalanine (F) at position 129 i.e., Y129F [270]. Interestingly, the CYP51 enzyme was shown to be highly regulated by iron in *A. fumigatus* [268,279].

Figure 5. Azoles and echinocandin antifungal drugs and their mechanism of actions: An illustration of two main classes of antifungal drugs used clinically and how they affect the fungal cell of *C. albicans*. (**A**) Echinocandins, e.g., caspofungin, inhibit β-(1-3)-D-glucan synthase in the cell membrane, which leads to disruption in cell wall integrity. (**B**) Azoles, e.g., fluconazole, inhibit Erg11/CYP51 F5, which blocks the production of ergosterol, leading to the accumulation of toxic sterol intermediates. **Δ** indicates where iron starvation or depletion may contribute to increased susceptibility to azole antifungals.

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