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Iron homeostasis—Achilles' heel of *Aspergillus fumigatus*?

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The opportunistic fungal pathogen *Aspergillus fumigatus* adapts to iron limitation by upregulation of iron uptake mechanisms including siderophore biosynthesis and downregulation of iron-consuming pathways to spare iron. These metabolic changes depend mainly on the transcription factor HapX. Consistent with the crucial role of iron in pathophysiology, genetic inactivation of either HapX or the siderophore system attenuates virulence of *A. fumigatus* in a murine model of aspergillosis. The differences in iron handling between mammals and fungi might serve to improve therapy and diagnosis of fungal infections.

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Introduction

Owing to its capacity to mediate electron transfer and acid–base reactions, iron is an essential nutrient for all eukaryotes and nearly all prokaryotes [1]. Either alone, or incorporated into iron–sulfur clusters or heme, this metal is an indispensable cofactor for a variety of cellular processes including respiration, amino acid metabolism, and biosynthesis of DNA and sterols. However, excess iron has the potential to catalyze the formation of cell-damaging reactive oxygen species [2]. Inversely, detoxification of oxidative stress depends on iron as, for example, catalases and peroxidases require heme as cofactor, which further underlines the complex intertwining of iron metabolism and oxidative stress. Despite its high abundance in the Earth's crust, the bioavailability of iron is very limited owing to its oxidation into insoluble ferric hydroxides by atmospheric oxygen. Furthermore, the mammalian innate immune system restricts iron availability to microbial invaders via a variety of mechanisms such as iron scavenging by transferrin or lactoferrin [3,4]. To overcome iron limitation and to avoid iron excess, all organisms and in particular pathogens have developed tightly regulated mechanisms to balance

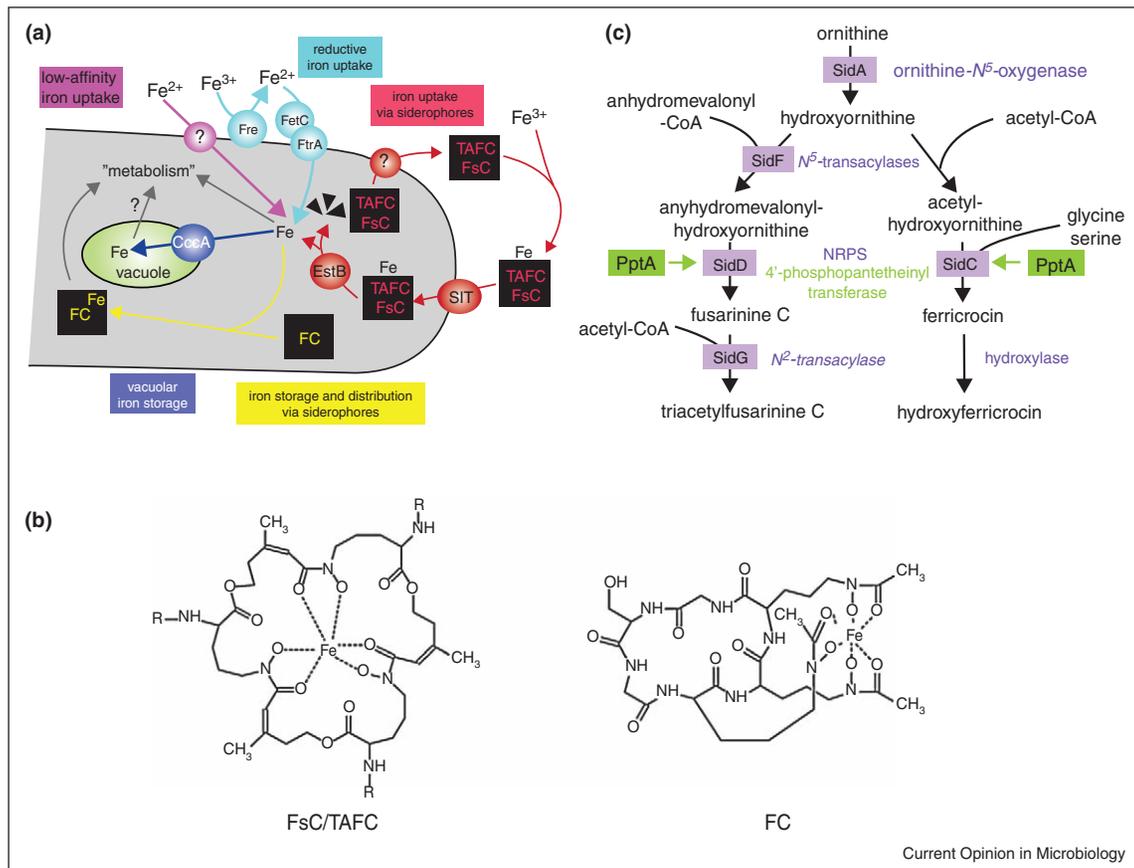
acquisition, storage and consumption of iron. In addition, iron starvation serves as a stimulus of iron-independent virulence determinants in pathogens. Consequently, the control of access to iron is one of the central battlefields on which the outcome of infection is decided.

Aspergillus fumigatus is a ubiquitous saprophytic fungus, which has become the most common air-borne fungal pathogen of humans [5]. Clinical manifestations range from allergic reactions to life-threatening invasive disease, termed aspergillosis, particularly in immuno-compromised patients. This review summarizes the current knowledge on iron homeostasis-maintaining mechanisms of *A. fumigatus* and their role in virulence.

Iron acquisition and storage

Control of iron uptake is considered the major iron homeostatic mechanism in *A. fumigatus* and other fungi because iron excretion systems have not been identified to date [6]. In contrast to various bacterial and some fungal pathogens [7,8], *A. fumigatus* lacks specific uptake systems for host iron sources such as heme, ferritin, or transferrin [9]. Instead iron supply is ensured by low-affinity ferrous iron acquisition as well as two high-affinity iron uptake systems, reductive iron assimilation (RIA) and siderophore-assisted iron uptake [9] (Figure 1a). At the molecular level, low-affinity iron uptake has been characterized in *Saccharomyces cerevisiae* but not in any other fungal species. The involved permeases transport not only ferrous iron, but also other metals such as copper and zinc [1]. RIA starts with reduction of ferric iron sources to the more soluble ferrous iron by plasma membrane-localized ferrireductases [10]. Subsequently, the ferrous iron is re-oxidized and imported by a protein complex consisting of the ferroxidase FetC and the iron permease FtrA. Siderophores are low molecular mass, ferric iron-specific chelators. *A. fumigatus* excretes two different siderophores, fusarinine C (FsC) and triacetyl-fusarinine C (TAFC), to mobilize extracellular iron (Figure 1b). The ferri-forms of FsC and TAFC are taken up by siderophore-iron transporters (SIT). SIT constitute a subfamily of the major facilitator protein superfamily acting most probably as proton symporters energized by the plasma membrane potential [11,12]. SIT-mediated iron uptake appears to be universally conserved in the fungal kingdom, even in species not producing siderophores such as *S. cerevisiae*, *Candida* spp. and *Cryptococcus neoformans* [6,12–14]. Possible reasons are the solubility and therefore high energy-status of siderophore-chelated iron and the putative role of 'stealing' siderophores in microbial warfare. For intracellular release of iron, TAFC and FsC are hydrolyzed, partly by the esterase EstB [15].

Figure 1



A. fumigatus mechanisms for iron uptake and storage. **(a)** Schematic summary of iron uptake and storage mechanisms. **(b)** Siderophore structures. R = H in FcS and R = acetyl in TAFC; the hydroxylation site in Fc is unknown. **(c)** Siderophore biosynthetic pathway. See text for details.

Siderophore-mediated iron uptake is conserved in most bacterial and some plant species. An exclusive feature of fungi, however, is the presence of intracellular siderophores. *A. fumigatus* possesses two different intracellular siderophores (Figure 1b), hyphal ferricrocin (FC) and conidial hydroxyferricrocin (HFC), for distribution and storage of iron [16[•],17[•]]. Additionally, *A. fumigatus* probably employs vacuolar iron storage, as indicated by the iron-inducible expression of CccA [18], the ortholog of the vacuolar iron importer Ccc1p of *S. cerevisiae* [1[•]]. In contrast to bacteria, plants and animals, however, fungi lack ferritin-mediated iron storage and detoxification.

Siderophore biosynthesis

FcS is a cyclic tripeptide consisting of three N⁵-anhydromevalonyl-N⁵-hydroxyornithine residues linked by ester bonds, TAFC is the N²-acetylated FcS, FC is a cyclic hexapeptide with the structure Gly-Ser-Gly-(N⁵-acetyl-N⁵-hydroxyornithine)₃ and HFC is hydroxylated FC [6]. The siderophore biosynthetic pathway characterized by reverse genetics is shown in Figure 1c. The first committed step in the biosynthesis of all four siderophores is hydroxylation of ornithine catalyzed by the

ornithine monooxygenase SidA. Subsequently, the pathways for biosynthesis of extracellular and intracellular siderophores split owing to the transfer of different acyl-groups to N⁵-hydroxyornithine: an acetyl group is transferred via an unknown enzyme to form intracellular siderophores and anhydromevalonyl is transferred by transacylase SidF to form extracellular siderophores. Assembly of FcS and FC is catalyzed by two different non-ribosomal peptide synthetases (NRPS), SidD and SidC, respectively. TAFC and HFC are formed by SidG-mediated N²-acetylation of FcS and hydroxylation of FC, respectively. Additionally, the 4'-phosphopantetheinyl transferase PptA is essential for siderophore biosynthesis because NRPS, along with polyketide synthetases and the lysine-biosynthetic α -aminoacidate reductase requires activation by this enzyme [19,20].

Biological functions of siderophores

Genetic elimination of extracellular siderophores (Δ sidF and Δ sidD mutants) decreases growth, conidiation and oxidative stress resistance under iron limited, but not iron sufficient conditions where other iron acquisition systems can compensate for the lack of siderophores [16[•]].

Elimination of intracellular siderophores ($\Delta sidC$ mutant) reduces conidiation and blocks sexual development (as shown in *A. nidulans*) owing to the role of FC in intracellular iron transport from substrate-contacting hyphae into aerial hyphae [16[•],17[•],21]. The reduced intracellular iron supply causes conidial iron shortage, which impairs iron-dependent enzymes such as catalase A and consequently decreases conidial resistance to oxidative stress [16[•],17[•]]. Moreover, such conidia show delayed germination during iron starvation owing to the lack of conidial iron storage [16[•]]. Ablation of the entire siderophore system ($\Delta sidA$ mutant) combines the defects caused by inactivation of either extracellular or intracellular siderophore biosynthesis and renders *A. fumigatus* extremely sensitive to iron starvation [9,16[•]].

Both extracellular and intracellular siderophores contribute to pathogenic growth because elimination of the entire siderophore system ($\Delta sidA$ mutant) results in absolute avirulence of *A. fumigatus* in a murine model of invasive pulmonary aspergillosis [9,22], while deficiency in either extracellular ($\Delta sidF$ or $\Delta sidD$ mutants) or intracellular siderophores ($\Delta sidC$ mutants) causes partial attenuation of virulence [16[•]]. Blocking TAFC production, while concomitantly increasing FsC production ($\Delta sidG$ mutant) affects neither growth nor virulence, indicating that the structural differences between these two siderophores do not play a role in these processes [16[•]]. Consistent with a role in iron acquisition during infection, the *A. fumigatus* siderophores are able to remove iron from host proteins, such as transferrin [23,24].

Genetic inactivation of RIA ($\Delta ftrA$ mutant) does not affect virulence of *A. fumigatus* [9]. Nevertheless, several lines of evidence indicate that RIA also plays a role during infection: (i) elimination of extracellular siderophores causes only partial attenuation of virulence, (ii) genome-wide expression profiling revealed induction of both the siderophore system and RIA during initiation of murine infection [25], and (iii) mutants lacking both RIA and the siderophore system ($\Delta ftrA\Delta sidA$ double mutant) are unable to grow unless supplemented with

siderophores or extremely high iron concentrations to fuel low-affinity iron uptake [9]. Of note, RIA has been shown to be crucial for virulence of fungi that do not produce siderophores, such as *C. albicans* and *C. neoformans* [26,27].

Restoration of conidial HFC content by supplementation with FC during conidiation partially cures the virulence defect of $\Delta sidA$ conidia [16[•]]. This demonstrates a crucial role of the conidial siderophore during initiation of infection, most probably owing to its importance for germination and oxidative stress resistance.

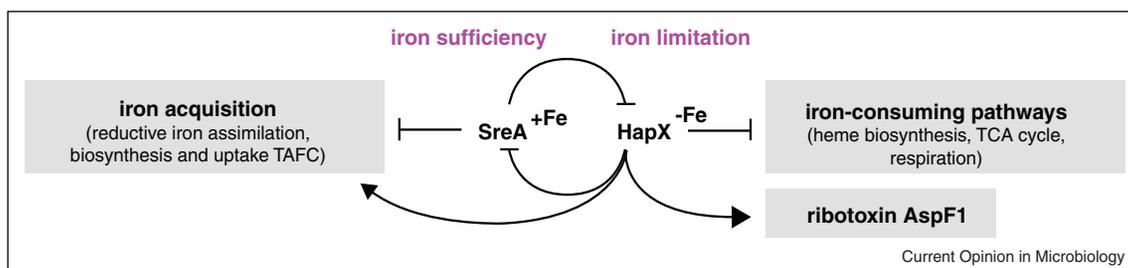
Defects in the siderophore system decrease intracellular growth and survival of *A. fumigatus* after phagocytosis by murine alveolar macrophages, which represent the first line of defense in the lung during pulmonary aspergillosis [28]. Consistent with these findings, siderophore-deficiency alters the immune response of murine macrophages against infection with *A. fumigatus* [29]. Similarly, the siderophore system is also important for virulence of *Histoplasma capsulatum*, a dimorphic fungal pathogen that replicates in the yeast form within macrophages [30]. Taken together, these data demonstrate that the siderophore system is crucial not only for extracellular but also for intracellular growth.

The evolutionary conserved role of iron in fungal virulence is underlined by the indispensable role of siderophores in various other experimental models of aspergillosis, that is, a murine cutaneous model, *Drosophila melanogaster*, and *Galleria mellonella* [31–33], as well as various phytopathogenic ascomycetes [34].

Regulation of iron homeostasis and its role in virulence

In *A. fumigatus*, iron starvation causes extensive transcriptional remodeling that is mediated by the two central transcription factors, SreA and HapX (Figure 2) [18,35[•]]. The DNA-binding GATA-factor SreA represses RIA and the siderophore system during iron sufficiency in order to avoid toxic effects. The bZip-transcription factor HapX physically interacts with the DNA-binding CCAAT-binding complex (as shown in *A. nidulans* [36]) and represses

Figure 2



Iron regulation in *A. fumigatus*.

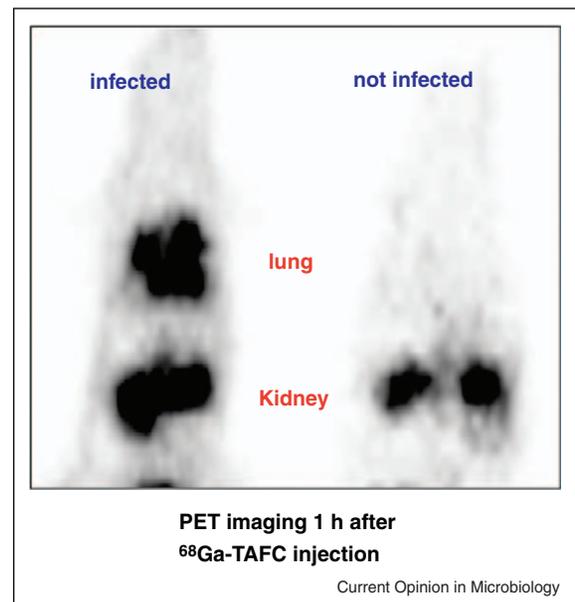
iron-consuming pathways such as heme biosynthesis, respiration and ribosome biogenesis during iron starvation to spare iron [35[•]]. Furthermore, HapX activates synthesis of the ribotoxin AspF1 and siderophores, the latter partly by ensuring a supply of the precursor, ornithine [35[•]]. SreA and HapX are interconnected in a negative feedback loop: SreA represses expression of *hapX* during iron sufficiency, while HapX represses *sreA* during iron starvation. In *A. nidulans*, inactivation of both regulators is synthetically lethal underlining the importance of iron metabolism for cellular survival [36]. In agreement with the expression pattern and mode of action, detrimental effects of inactivation of SreA or HapX are confined to growth during iron sufficiency or starvation, respectively. Deficiency in HapX, but not SreA, attenuates virulence of *A. fumigatus* in a murine model of aspergillosis [18,35[•]], which underlines the crucial role of adaptation to iron limitation in virulence. Most fungal species possess orthologs of SreA and HapX, and the crucial role of HapX orthologs in virulence has been demonstrated in *C. albicans* and *C. neoformans* [6,37–39]. A notable exception is the prototypical yeast *S. cerevisiae*, which employs entirely different regulators [1[•]]. Owing to the central metabolic role of iron, iron regulation is interconnected with various other regulatory circuits in *Aspergilli*, for example, pH regulation, gluconeogenesis, zinc metabolism, and oxidative stress response [40–43]. Recently, deficiency in the transcription factor AcuM was shown to impair both gluconeogenesis and high-affinity iron uptake in *A. fumigatus*, whereby only the latter was suggested to be responsible for the virulence defect caused by AcuM-deficiency [41]. Various other metabolic links are expected to be identified in the future.

Conclusions and perspectives

The attenuated virulence caused by defects in siderophore biosynthesis or HapX strongly suggests that *A. fumigatus* faces iron limitation during mammalian infection. This concept is supported by the finding that increased bone marrow iron stores represent an independent risk factor for invasive aspergillosis [44]. Moreover, human protection against *A. fumigatus* includes growth inhibition by polymorphonuclear leukocytes via lactoferrin-mediated iron depletion and possibly siderocalin-mediated scavenging of siderophores [45,46].

Aspergillosis is difficult to diagnose and treat, which is reflected by the high mortality rates that continue to be associated with this disease [5]. The essentiality of iron for fungal virulence and the differences in iron acquisition mechanisms between mammals and fungi such as *Aspergillus* spp. might help to improve therapy and diagnosis of fungal infections. Specifically, the fungal siderophore biosynthetic pathway represents a promising target for selective therapeutic intervention. Furthermore, SIT constitute one of few protein families that are unique to fungi and are not present in prokaryotes or other eukaryotes [47]. Thus, this protein family is a promising

Figure 3



PET imaging of invasive pulmonary aspergillosis in a rat model using ⁶⁸Ga-TAFC. Images demonstrating accumulation of ⁶⁸Ga in infected lungs were taken one hour after injection of ⁶⁸Ga-TAFC into the femoral vein. Kidneys are labeled in infected and non-infected animals owing to renal excretion of ⁶⁸Ga-TAFC. This figure was reprinted by permission of the Society of Nuclear Medicine from [51[•]].

drug target, and it could also be used to target drug delivery specifically to the fungus by a Trojan horse approach [48], in which antifungal agents are covalently attached to siderophores and selectively imported by the infecting fungus. The potential of iron chelation therapy is indicated by the synergistic effect of iron chelators and antifungal drugs that has been demonstrated both *in vitro* and in a murine aspergillosis model [49,50[•]]. Moreover, the recently demonstrated PET (Positron Emission Tomography) imaging of invasive pulmonary aspergillosis in a rat model, based on fungal accumulation of TAFC-chelated ⁶⁸Gallium (Figure 3), underlines the potential of utilizing siderophores for the diagnosis of fungal infections [51[•]].

The understanding of the role of iron in fungal infections clearly has advanced enormously in recent years. Nevertheless, its potential application in treatment and diagnosis of fungal infections still requires deeper insights.

Conflicts of interest

No conflicting interests.

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