Iron – a key nexus in the virulence of Aspergillus fumigatus

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INTRODUCTION

Iron is an essential nutrient for all eukaryotes and nearly all prokaryotes (Kaplan and Kaplan, 2009). As mono or diiron center as well as incorporated into heme or iron–sulfur clusters, this metal is an indispensable cofactor for a variety of cellular processes including electron transport, amino acid metabolism, and biosynthesis of DNA and sterols. Nevertheless, iron excess has the potential to catalyze the formation of cell-damaging reactive oxygen species (Halliwell and Gutteridge, 1984). The complex intertwining of iron metabolism and oxidative stress is emphasized by the iron-dependence of detoxification of oxidative stress as, e.g., catalases and peroxidases require heme as cofactor. Despite its high abundance in the Earth’s crust, the bioavailability of iron is low owing to its oxidation into sparingly soluble ferric (Fe(III)) hydroxides by atmospheric oxygen. To ensure iron supply but to avoid iron toxicity, all organisms evolved sophisticated mechanisms to balance acquisition, storage, and consumption of iron. The control over access to iron is one of the central battlefields during infection as pathogens have to “steal” the iron from the host. Moreover, the mammalian innate immune system restricts access to iron by pathogens via a variety of mechanisms (Ganz, 2009; Weinberg, 2009).

Aspergillus fumigatus is a ubiquitous saprophytic fungus, which has become the most common air-borne fungal pathogen of humans (Tekaia and Latge, 2005). Clinical manifestations range from allergic reactions to life-threatening invasive disease, termed aspergillosis, particularly in immuno-compromised patients. The identification and functional characterization of 24 genes that are involved in iron homeostasis in A. fumigatus and/or Aspergillus nidulans, respectively, revealed significant insights into iron metabolism and its regulation (Table 1). A. nidulans is a less virulent A. fumigatus relative and longstanding genetic model organism. Inactivation of 10 of the 19 A. fumigatus genes caused defects in virulence. All of the virulence-associated genes are transcriptionally upregulated during iron starvation and encode functions that are important for survival during iron starvation, which emphasizes the crucial role of adaptation to iron starvation in virulence. This review summarizes the current knowledge on iron homeostasis and its role in virulence in Aspergillus spp.

IRON ACQUISITION

As microorganisms are believed to lack mechanisms for iron excretion, control of iron uptake is considered the major iron homeostatic mechanism (Haas et al., 2008). In contrast to various bacterial and fungal pathogens (Ratl edge and Dover, 2000; Almeida et al., 2009), both A. fumigatus and A. nidulans lack systems for direct uptake of host iron sources such as heme, ferritin, or transferrin (Eisendle et al., 2003; Schrettl et al., 2004a).

**Table 1**

| Gene       | Function                                      | A. fumigatus | A. nidulans |
|------------|-----------------------------------------------|--------------|-------------|
| HapX       | Iron-repressing factor                        |              |             |
| SreA       | Iron-uptake regulating factor                 |              |             |
| SrbA       | Extra and intracellular siderophores          |              |             |
| AspF1      | Iron-consuming pathway                        |              |             |
| Siderophores|                                               |              |             |
| Dormancy   |                                               |              |             |

**Abbreviations:** CBC, CCAAT-binding complex; FC, ferricrocin; FsC, fusarinine C; RIA, reductive iron assimilation; SB, siderophore biosynthesis; SIT, siderophore-iron transporter; TAFC, triacetylfusarinine C; TF, transcription factor.

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**References**: Haas et al., 2008; Kaplan and Kaplan, 2009; Ganz, 2009; Weinberg, 2009; Tekaia and Latge, 2005; Eisendle et al., 2003; Schrettl et al., 2004a; Ratledge and Dover, 2000; Almeida et al., 2009.
Both *Aspergillus* species employ low-affinity ferrous ($\text{Fe}^{2+}$) iron acquisition as well as siderophore-assisted iron uptake, a high-affinity ferric iron uptake system (Eisendle et al., 2003; Schrettl and Haas, 2011). In contrast to *A. nidulans*, *A. fumigatus* possesses a second high-affinity iron uptake system, termed reductive iron assimilation (RIA). Schemes of the mechanisms for iron uptake and storage employed by *Aspergillus* spp. are found in recently published reviews (Haas et al., 2008; Schrettl and Haas, 2011).

## Table 1 | Functionally analyzed proteins involved in iron homeostasis in *A. fumigatus* and *A. nidulans*.

| Protein | Gene | Function | Gene deletion-caused defect in iron metabolism | Expression | Virulence | Reference |
|---------|------|----------|-----------------------------------------------|------------|-----------|-----------|
| **ENZYMES/TRANSPORTERS INVOLVED IN RIA (3)** | | | | | | |
| FetC | AFUA_5G03790 | Ferroxidase | RIA | $\text{Fe}^3+$ | $\text{Fe}$ | $\text{Fe}$ | Schrettl et al. (2004a) |
| FreB | AFUA_1G17270 | Ferric reductase | RIA | $\text{Fe}^3+$ | $\text{Fe}$ | $\text{Fe}$ | Blatzer et al. (2011b) |
| FtrA | AFUA_5G03800 | Iron permease | RIA | $\text{Fe}^3+$ | $\text{Fe}$ | $\text{Fe}$ | Schrettl et al. (2004a) |
| **ENZYMES INVOLVED IN SB (10)** | | | | | | |
| EstA | AFUA_3G03660 | TAF esterase | TAF hydrolysis after uptake (partial) | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Schrettl et al. (2004a) |
| NpgA/PptA§ | AFUA_2G08590 | Phosphopantetheinyl transferase | Entire SB (all NRPS and polyketide synthetases) | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Oberegger et al. (2003) |
| SidA§ | AFUA_2G07680 | Ornithine monooxygenase | Entire SB | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Schrettl et al. (2004a) |
| SidC§ | AFUA_1G17200 | FC NRPS | FC biosynthesis | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Schrettl et al. (2007) |
| SidD | AFUA_5G03650 | FSC NRPS | FSC and TAFC biosynthesis | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Schrettl et al. (2007) |
| SidF | AFUA_3G03420 | Transacylase | FSC and TAFC biosynthesis | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Schrettl et al. (2007) |
| SidG | AFUA_3G03400 | Transacetylase | TAFC biosynthesis (but increased FSC biosynthesis) | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Schrettl et al. (2007) |
| **SITs (2)** | | | | | | |
| MirA | AN7800 | Enterobactin transporter | | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Schrettl et al. (2004a) |
| MirB | AN8540 | TAF transporter | | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Schrettl et al. (2004a) |
| **REGULATORY PROTEINS (9)** | | | | | | |
| AcuM§ | AFUA_2G12330 | Zr2-Cys6 TF | Repression of iron uptake including SB and RIA | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Liu et al. (2010) |
| HapB* | AN7545 | Subunit of the CBC | See HapX | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Hortschansky et al. (2007) |
| HapC* | AN4034 | Subunit of the CBC | See HapX | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Hortschansky et al. (2007) |
| HapE* | AN6492 | Subunit of the CBC | See HapX | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Hortschansky et al. (2007) |
| HapX§ | AFUA_5G03920 | bZip-TF | Repression of iron consumption, activation of iron uptake | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Schrettl et al. (2010a) |
| MpkA | AFUA_4G13720 | MAP kinase A | Repression of SB | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Jain et al. (2011) |
| PacC* | AFUA_3G11970 | Cy2-His2$_2$ TF | Activation of TAFC biosynthesis in alkaline pH | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Eisendle et al. (2004) |
| SrbA | AFUA_2G01260 | bHLH-LZ TF | Activation of iron uptake including SB and RIA | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Blatzer et al. (2011a) |
| SreA§ | AFUA_5G11260 | GATA TF | Repression of iron uptake including SB and RIA | $\text{Fe}$ | $\text{Fe}$ | $\text{Fe}$ | Schrettl et al. (2008) |

1 Unmarked, function analyzed only in *A. fumigatus*; *, function analyzed only in *A. nidulans*; §, function is conserved in *A. nidulans* and *A. fumigatus*;˚, iron regulatory function found only in *A. fumigatus* but not in *A. nidulans*.  
2 $\text{Fe}$, transcriptional upregulation during iron starvation; $\text{Fe}$, transcriptional upregulation during iron sufficiency; $\text{Fe}$, constitutively expressed.  
3 $\text{Fe}$, virulent; $\text{Fe}$, partially attenuated virulent; $\text{Fe}$, avirulent.  
4 na, not analyzed.
other metals, such as copper and zinc (Kaplan and Kaplan, 2009).

**REDUCTIVE IRON ASSIMILATION**

Reductive iron assimilation starts with reduction of ferric iron sources to the more soluble ferrous iron by plasma membrane-localized metalloreductases (Kosman, 2010). A. fumigatus encodes 15 putative metalloreductases indicating possible redundancy of this enzyme system. The metalloreductase FreB has recently been shown to be involved in RIA (Blatzer et al., 2011b). The reduced ferrous iron is re-oxidized and imported by a protein complex consisting of the ferroxidase FetC and the iron permease FtrA (Schrettl et al., 2004a).

**SIDEROPHORE-MEDIATED IRON UPTAKE**

The siderophores produced by A. nidulans and A. fumigatus are shown in Figure 1. Both fungal species excrete two siderophores, fusarinine C (FsC) and its derivative triacetylfusarinine C (TAFC), to mobilize extracellular iron. The ferri-forms of FsC and TAFC are taken up by siderophore-iron transporters (SIT), which constitute a subfamily of the major facilitator protein superfamily. SIT act most likely as proton symporters energized by the plasma membrane potential (Haas et al., 2003; Philpott and Protchenko, 2008). 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 (Schrettl et al., 2004b; Haas et al., 2008; Jung and Kronstad, 2008; Philpott and Protchenko, 2008; Nevitt and Thiele, 2011). A likely reason is the dramatically increased solubility and therefore bioavailability of iron chelated by siderophores. Moreover, siderophores might play a role in microbial warfare as chelation of environmental iron by siderophore-types that are not recognized by competitors might be used to starve competitors of iron. This is counteracted by evolving transporters that recognize xenosiderophores, i.e., siderophores that are not produced by the organism, which enables “stealing” of siderophores. This scenario is supported by the fact that most siderophore-producing bacteria and fungi possess xenosiderophore-specific SITs (Haas et al., 2008). A. fumigatus and A. nidulans encode 10 and 7 putative SITs, respectively (Haas et al., 2008). Heterologous expression in a S. cerevisiae mutant lacking high-affinity iron uptake indicated that the A. nidulans SITs MirA and MirB transport the bacterial siderophore enterobactin and TAFC, respectively (Haas et al., 2003).

After uptake, the intracellular release of iron from TAFC and FsC involves hydrolysis of the siderophore backbones by the esterase EstB (Kragl et al., 2007).

**IRON STORAGE**

Extracellular siderophores are employed by most bacterial and some plant species. In contrast, intracellular siderophores are only found in siderophore-producing fungi. A. fumigatus produces two different intracellular siderophores (Figure 1), ferricrocin (FC) for hyphal iron storage and distribution and its derivative hydroxyferricrocin (HFC) for conidial iron storage (Schrettl et al., 2007; Wallner et al., 2009). A. nidulans lacks HFC and employs FC for both hyphal and conidial iron storage (Eisendle et al., 2003). Additionally, the iron-inducible expression of CccA, the ortholog of the vacuolar iron importer Ccc1p from S. cerevisiae (Kaplan and Kaplan, 2009), indicates vacuolar iron storage in A. fumigatus (Schrettl et al., 2008). In contrast to bacteria, plants, and animals, fungi lack ferritin-mediated iron storage and detoxification.

**SIDEROPHORE BIOSYNTHESIS**

Fusarinine C consists of three N\(^{3}\)-anhydromevalonyl-N\(^{3}\)-hydroxynorleucine residues cyclically linked by ester bonds. TAFC is the N\(^{2}\)-acetylated FsC. FC is a cyclic hexapeptide with the structure Gly-Ser-Gly-(N\(^{5}\)-acetyl-N\(^{5}\)-hydroxyornithine)\(^{3}\) and HFC is the hydroxylated FC (Haas et al., 2008). The siderophore biosynthesis (SB) pathway was characterized by reverse genetics and is shown in Figure 2. The first committed step in the biosynthesis of all four siderophores is the hydroxylation of ornithine catalyzed by the ornithine monooxygenase SidA (Eisendle et al., 2003; Schrettl et al., 2004a). Subsequently, the pathways for biosynthesis of extra and intracellular siderophores split. For extracellular SB the transacylase SidF transfers anhydromevalonolyl to hydroxynorleucine (Schrettl et al., 2007). The required anhydromevalonolyl-CoA moiety is derived from mevalonate by CoA-ligation and

![Figure 1](https://example.com/figure1.png)
The iron link of *Aspergillus fumigatus* virulence

### FIGURE 2 | Siderophore biosynthesis (in purple) and its links to the isoprenoid biosynthesis (in green) as well as ornithine/arginine metabolism (in blue). The enzymes, boxed in respective colors, are described in the text and Table 1. Enzymatic steps transcriptionally upregulated during iron starvation are marked by red arrows. Broken arrows denote reactions involving more than one enzyme.

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dehydration catalyzed by SidI and SidH, respectively (Yasmin et al., 2011). The acetylation of hydroxyornithine for intracellular SB involves two transacetylases, the constitutively expressed SidL and an unidentified enzyme, the activity of which is upregulated by iron starvation (Blatzer et al., 2011c). Assembly of FsC and FC is catalyzed by two different non-ribosomal peptide synthetases (NRPS), SidD and SidC, respectively. TAFC and HFC are formed by SidG-mediated N^2^-acetylation of FsC and hydroxylation of FC, respectively (Eisendle et al., 2003; Schrettl et al., 2007). NRPS, polyketide synthases, and the lysine-biosynthetic α-aminoadipate reductase depend on activation by the 4′-phosphopantetheinyl transferase. Consistently, the 4′-phosphopantetheinyl transferases NpgA and PptA are essential for SB in *A. nidulans* and *A. fumigatus*, respectively (Oberegger et al., 2003; Blatzer et al., 2011c). Moreover, NpgA/PptA is not exclusively involved in SB. In contrast to *A. fumigatus* and *A. nidulans*, SidA ortholog-encoding genes are clustered with siderophore NRPS in various other fungi, e.g., *Ustilago maydis* and *Neurospora crassa* (Haas et al., 2008). The genes encoding FtrA and FetC form a gene cluster with a common promoter region.

### DEFECTS CAUSED BY SIDEROPHORE-DEFICIENCY

Genetic elimination of extracellular siderophores (ΔsidF and ΔsidD mutants) decreases growth, conidiation, and oxidative stress resistance during iron limitation but not during iron sufficiency, which enables compensation by other iron acquisition systems (Schrettl et al., 2007). Elimination of intracellular siderophores (ΔsidC mutant) reduces conidiation and blocks sexual development (as shown in *A. nidulans*) due to the role of FC in intracellular iron transport from substrate-contacting hyphae into aerial hyphae (Eisendle et al., 2006; Schrettl et al., 2007; Wallner et al., 2009). FC-deficiency decreases the conidial iron content by about 50%, which impairs iron-dependent enzymes such as aconitase and catalase A, and thereby decreases conidial size and conidial resistance to oxidative stress (Schrettl et al., 2007; Wallner et al., 2009). Moreover, the lack of FC-mediated iron storage (ΔsidC mutants) delays germination during iron starvation (Schrettl et al., 2007). Inactivation of the entire siderophore system (ΔsidA mutant) combines the defects caused by inactivation of either extra or intracellular SB and renders *A. fumigatus* extremely sensitive to iron starvation (Schrettl et al., 2004a, 2007).
Both extracellular and intracellular siderophores are crucial for virulence as elimination of the entire SB ($\Delta sidA$ mutant) results in an absolute avirulence of $A.\ fumigatus$ in a murine model of invasive pulmonary aspergillosis (Schrettl et al., 2004a; Hissen et al., 2005), while deficiency in either extracellular ($\Delta sidI, \Delta sidH, \Delta sidF,$ or $\Delta sidD$ mutants) or intracellular siderophores ($\Delta sidC$ mutants) causes partial attenuation of virulence (Schrettl et al., 2007; Yasmin et al., 2011). Conidial FC appears to play a particularly crucial role during initiation of infection because restoration of the conidial HFC content by supplementation with FC during conidiation partially cures the virulence defect of $\Delta sidA$ conidia (Schrettl et al., 2007). $SidG$-deficiency, which eliminates TAFc production with concomitant increase of FsC production, affects neither growth nor virulence, indicating that the structural differences between these two siderophores do not play a role in these settings (Schrettl et al., 2007). Consistent with a role in iron acquisition during infection, $A.\ fumigatus$ siderophores are able to remove iron from host sources, such as transferrin (Hissen et al., 2004; Hissen and Moore, 2005).

Blocking RIA ($\Delta ftrA$ mutant) does not affect virulence of $A.\ fumigatus$ (Schrettl et al., 2004a). Nevertheless, a putative role of RIA in virulence is indicated by several lines of evidence: (i) elimination of extracellular siderophores causes only partial attenuation of virulence, (ii) 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 fueling low-affinity iron uptake (Schrettl et al., 2004a), and (iii) genome-wide expression profiling demonstrated induction of both the siderophore system and RIA during murine infection (McDonagh et al., 2008). Consistently, RIA has been shown to be crucial for virulence of the siderophore-lacking species $C.\ albicans$ and $C.\ neoformans$ (Ramanan and Wang, 2000; Jung et al., 2008).

The siderophore system is important not only for extra, but also for intracellular growth as 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 (Schrettl et al., 2010b). Furthermore, impairment of SB changes the immune response of macrophages after phagocytosis of $A.\ fumigatus$ (Seifert et al., 2008). In agreement, the siderophore system is also critical for virulence of $H.\ capsulatum$, a dimorphic fungal pathogen replicating in the yeast form within macrophages (Hwang et al., 2008). The evolutionary conserved role of siderophores in virulence has been confirmed in various other aspergillosis infection models, i.e., a murine cutaneous model, $Drosophila\ melanogaster$, and $Galleria\ mellonella$ (Ben-Ami et al., 2010; Chamilos et al., 2010; Slater et al., 2011). Moreover, SB is indispensable for the virulence of the various phytopathogenic ascomycetes (Oide et al., 2006; Greenshields et al., 2007). In contrast, SB is dispensable and RIA is essential for phytopathogenicity of $U.\ maydis$ (Mei et al., 1993; Eichhorn et al., 2006).
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FIGURE 3 | Iron regulation in Aspergillus spp. (A) Scheme of SreA- and HapX-mediated iron regulation. (B) Phenotypes of A. fumigatus SreAΔsreA and HapXΔhapX deficient mutant strains in 24 h/37˚C flask cultures. In contrast to the wild type (wt), ΔsreA mycelia are reddish colored during iron sufficiency due to accumulation of iron, heme, and FC (Schrettl et al., 2008, 2010a). Reddish colored during iron starvation due to accumulation of protoporphyrin IX, while ΔsreA mycelia are reddish colored during iron sufficiency due to accumulation of iron, heme, and FC (Schrettl et al., 2008, 2010a).

Iron toxicity (Schrettl et al., 2008). During iron starvation, the bZip-TF HapX represses iron-consuming pathways such as heme biosynthesis, respiration, and ribosome biogenesis to spare iron (Oberegger et al., 2001, 2002; Schrettl et al., 2008, 2010a). Furthermore, HapX activates synthesis of the ribotoxin AspF1 and siderophores in A. fumigatus, the latter partly by coordinating SB with supply of its precursor ornithine (Schrettl et al., 2010a). The metabolic deregulation caused by deficiency in either SreA or HapX causes reddish hyphal pigmentation (Figure 3). SreA and HapX are interconnected in a negative feed-back loop: SreA represses expression of hapX during iron sufficiency, while HapX represses sreA during iron starvation. Additionally, both SreA and HapX appear to be regulated posttranslationally by iron blocking HapX function and activating SreA function (Haas et al., 1999; Hortschansky et al., 2007). In S. pombe, posttranslational iron sensing by the HapX and SreA orthologs involves the monothiol glutaredoxin Grx4 (Mercier and Labbe, 2009; Jbel et al., 2011; Kim et al., 2011). In A. nidulans and A. fumigatus, inactivation of both HapX and SreA is synthetically lethal underlining the critical role of iron homeostasis in cellular survival (Hortschansky et al., 2007; Schrettl et al., 2008, 2010a). In agreement with their expression pattern and mode of action, detrimental effects of inactivation of SreA or HapX are confined to growth during iron sufficiency or starvation, respectively (Figure 3). Deficiency in HapX, but not SreA, attenuates virulence of A. fumigatus in murine models of aspergillosis (Schrettl et al., 2008, 2010a), which emphasizes the crucial role of adaptation to iron limitation in virulence. Most fungal species possess orthologs to SreA and HapX and the important role of HapX orthologs in virulence has been demonstrated in C. albicans and C. neoformans (Labbe et al., 2007; Haas et al., 2008; Jung et al., 2010; Hsu et al., 2011). Similar to A. fumigatus, the SreA ortholog Sfu1 is dispensable for systemic virulence of C. albicans (Chen et al., 2011). However, Sfu1 is crucial for persistence of this commensal in the iron-rich gut, which impressively illustrates the importance of adaptation to opposing conditions of iron availability for survival. Remarkably, the fungal prototype S. cerevisiae lacks orthologs of SreA, HapX, and SrB and employs entirely different regulators, Aft1/2 and Cth1/2, which are conserved only in closely related Saccharomycotina species (Haas et al., 2008; Kaplan and Kaplan, 2009).

INTERCONNECTION OF IRON METABOLISM WITH OTHER REGULATORY CIRCUITS: OXYGEN, REDOX PH, GLUCONEOGENESIS, MAP KINASE SIGNALING, ZINC

Due to the central metabolic role of iron, a variety of regulatory circuits affect cellular iron handling. As obligate aerobic organisms, Aspergilli rely on respiration, which is highly iron-dependent. Therefore, oxygen supply largely influences iron metabolism and vice versa. Recently, proteomic analysis of A. fumigatus revealed that hypoxia increases the production of proteins involved in glycolysis, the TCA-cycle, and respiration, which is paralleled by increased cellular iron, heme, copper, and zinc contents (Vodisch et al., 2009). The increase in iron/heme is attributable to the iron/heme-dependence of the TCA-cycle and respiration. In A. fumigatus, hypoxic adaptation involves SrB, a member of the “sterol regulatory element binding protein (SREBP)” TF family, which is conserved in most eukaryotes (Willger et al., 2008). These TFs are activated by cellular sterol-depletion to maintain sterol homeostasis (Bien and Espenshade, 2010). In A. fumigatus, SrB-deficiency decreases the cellular ergosterol content.
and resistance against azole drugs and blocks hypoxic growth as well as virulence (Willger et al., 2008). Recently, SrbA was found to activate siderophore-mediated iron uptake in response to hypoxia and iron starvation in part by transcriptional activation of HapX (Blätzer et al., 2011a). In agreement with SrbA being involved in iron homeostasis, defects in hypoxic growth and azole resistance caused by SrbA-deficiency are at least partly cured by increased iron supplementation and in particular by de-repression of iron uptake via simultaneous inactivation of SreA (Blätzer et al., 2011a). SrbA is transcriptionally upregulated during hypoxia and iron starvation, in both cases likely in response to sterol-depletion and autoregulation as sterol biosynthesis depends on both oxygen and iron. During iron starvation, consumption of the sterol intermediate mevalonate by SB might play an additional role (see above). In agreement, the transcriptional activation of SrbA during iron starvation is independent of SreA and HapX. These data indicate that A. fumigatus senses iron not only via HapX and SreA but also via ergosterol biosynthesis and SrbA. Taken together, SrbA coordinates ergosterol biosynthesis and iron metabolism to mediate hypoxia responses and azole resistance. Growth defects during iron starvation of respective gene deletion mutants indicate similar functions in iron homeostasis of the SrbA orthologs in S. pombe and C. neoformans (Hughes et al., 2005; Chang et al., 2007). Moreover, the SrbA ortholog is also crucial for virulence in C. neoformans (Chun et al., 2007). Consequently, the virulence defect of SrbA mutants is possibly attributable not only to the defects in adaptation to hypoxia, but also iron starvation. S. cerevisiae lacks an SrbA ortholog and the TFs mediating hypoxic adaptation (Hap1, Mot1, Rox1) are not conserved in Aspergillus (Willger et al., 2008), which might be explained by S. cerevisiae being a facultative anaerobe.

As shown in A. nidulans, HapX functions via physical interaction with the DNA-binding CCAAT-binding complex (CBC; Hortschansky et al., 2007). The CBC is a heterotrimeric DNA-binding complex, which is conserved in all eukaryotes. In A. nidulans, inactivation of either one of its subunits, Hap8, HapC, or HapE phenocopies HapX inactivation with respect to the defects in adaptation to iron starvation. However, the CBC has HapX-independent functions and is speculated to affect expression of about 30% of all genes. Consistently, CBC-deficiency results in decreased growth and sporulation during both iron sufficiency and starvation (Hortschansky et al., 2007). The mode of discrimination between HapX targets and the remaining CBC targets remains to be elucidated. As mentioned in the introduction, iron metabolism and oxidative stress are intimately intertwined. Therefore it is particularly interesting that, as shown in A. nidulans, the CBC senses the redox state of the cell via oxidation and thioredoxin-mediated reduction of evolutionary conserved thiol groups within the HapC histone fold motif (Thon et al., 2010). Oxidation blocks CBC formation and nuclear localization. In line with a role in redox regulation, CBC-deficiency impairs the oxidative stress response. The impact of iron availability on the oxidative stress detoxification system is indicated by iron starvation-mediated transcriptional downregulation of the heme-dependent hypthal catalase B (CatB) and upregulation by the Cu/Zn-superoxide dismutase (SodA; Oberegger et al., 2000, 2001). Excessive iron uptake caused by SreA-deficiency transcriptionally upregulates both enzymes (Oberegger et al., 2001).

The ambient pH impacts iron availability as alkaline conditions decrease iron solubility. In line, neutral compared to acidic conditions upregulate SB and uptake in A. nidulans mediated by the pH-reactive TF PacC (Elisendle et al., 2004). Similarly, PacC orthologs mediate upregulation of high-affinity iron uptake – in these species RIA – during alkaline conditions in S. cerevisiae, C. albicans, and C. neoformans (Lamb et al., 2001; Back et al., 2008). Virulence of C. albicans but not C. neoformans depends on its PacC ortholog, which is most likely attributable to the occupation of different host niches by these two pathogens (Nobile et al., 2008; O’Meara et al., 2010).

Interestingly, deficiency in the TF AcuM, which is required for gluconeogenesis, decreases siderophore production in A. fumigatus, but not in A. nidulans, and attenuates virulence in A. fumigatus (Liu et al., 2010). Though it is unclear if its effects are direct, AcuM appears to transcriptionally repress SreA.

Recently, iron starvation was found to trigger phosphorylation and nuclear localization of the A. fumigatus mitogen-activated protein kinase (MAPK) MpkA, which is involved in maintaining cell wall integrity, protection against ROS, and secondary metabolism (Jain et al., 2011). Moreover, MpkA-deficiency increases siderophore production. The TF targeted by MpkA signaling remains to be identified. Remarkably, despite its dramatic effect on in vitro growth rate, MpkA-deficiency does not affect virulence of A. fumigatus (Valiante et al., 2008).

Similar to iron, zinc plays a critical role in a diverse array of biochemical processes, but excess of zinc is deleterious. Consequently, regulation of zinc homeostasis by the TF ZaFa is essential for virulence of A. fumigatus. Iron starvation causes zinc hypersensitive and therefore iron depletion changes cellular zinc handling by downregulating zinc uptake and upregulation of vacuolar zinc detoxification (Yasmin et al., 2009). HapX appears to play a critical role in coordination of zinc and iron homeostasis as its deficiency causes zinc hypersensitivity during iron starvation. These data demonstrate the importance of cellular metal balancing.

**CONCLUSION AND PERSPECTIVES**

The understanding of the role of iron in fungal pathogenicity has advanced enormously in recent years. Together with the transcriptional upregulation of the high-affinity iron acquisition systems during initiation of murine infection (McDonagh et al., 2008), the attenuated virulence caused by defects in SB or HapX confirms that A. fumigatus faces iron limitation during mammalian infection. Thus, human protection against A. fumigatus includes growth inhibition by polymorphonuclear leukocytes via lactoferrin-mediated iron depletion and possibly siderocalin-mediated scavenging of siderophores (Fluckinger et al., 2004; Zarember et al., 2007). On the other hand, increased bone marrow iron stores represent an independent risk factor for invasive aspergillosis (Kontoyiannis et al., 2007).

The current difficulties in diagnosis and treatment of aspergillosis are reflected by the high mortality rate of this infectious disease (Tekaya and Latge, 2005). Theessentiality of iron and the differences in iron handling between mammals and fungi
like Aspergillus might help to improve therapy and diagnosis of fungal infections. Specifically, the unique fungal siderophore system represents a promising target for selective therapeutic intervention. Noteworthy, STf constitute one of few protein families that are unique to fungi (Hsiang and Baille, 2003). Their absence in prokaryotes and other eukaryotes might enable specific inhibition or drug delivery during infection by a “Troyan horse” approach (Miller et al., 2009), whereby antifungal agents are covalently attached to siderophores and selectively imported by fungi.

Moreover, the enzymatic and regulatory links between siderophore and ergosterol biosynthetic pathways might be crucial for optimization of treatment of infections caused by siderophore-producing fungi. The potential of iron chelation therapy is indicated by the synergistic effect of iron chelators and antifungal drugs demonstrated in vitro and in a murine aspergillosis model (Zarembet et al., 2009; Ibrahim et al., 2010). Moreover, the recently demonstrated imaging of invasive pulmonary aspergillosis in a rat model, based on positron emission tomography (PET)-visualized fungal accumulation of TAFc-chelated 68Gallium, emphasizes the potential of siderophores in diagnosis of fungal infections (Petrik et al., 2010a,b).

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