Aspergillus fumigatus, pathogens that are responsible for the majority of opportunistic and Pirofski, 1999). In fact, virulence of the two major fungal groups defined and unique characteristics to cause disease, features associated clinical cases has significantly increased over the last decades, mainly based on modern medicine practices multiplying the number of immunosuppressed, susceptible individuals. Opportunistic fungi usually cannot thrive within the tissue of an immunocompetent individual. This suggests that they do not possess defined and unique characteristics to cause disease, features that have classically been coined as virulence factors (Casadevall and Pirofski, 1999). In fact, virulence of the two major fungal pathogens that are responsible for the majority of opportunistic infections, Candida albicans and A. fumigatus, appears to be multifactorial (Cassler, 1991; Latgé, 2001; Huber, 2004; Abad et al., 2010). This hampers the identification of specific targets against which chemotherapeutic compounds may be active. And indeed, current antifungal chemotherapy, which is mainly based on disrupting the integrity of the fungal cell membrane or wall (Hoehamer et al., 2010), is not satisfactory efficient. It has become evident that nutritional versatility, uptake mechanisms to assist in identifying novel targets of antifungal therapy. For instance, iron acquisition from host tissues has been proven to be important for virulence of several pathogens, among them fungi as C. neoformans, C. albicans, or A. fumigatus (Ramaman and Wang, 2000; Jung et al., 2008; Haas, 2012). In the latter, in vivo iron acquisition was shown to be dependent on the siderophore system and independent of the iron reductive assimilation pathway (Schmitt et al., 2004), establishing this process as a virulence attribute. This exemplifies how a deeper knowledge of the metabolic status and nutrient acquisition strategies within infected tissues sheds light on fungal virulence mechanisms to assist in identifying novel targets of antifungal therapy (Brock, 2009).

THE HOST REPRESENTS A DISTINCT ENVIRONMENT DURING ASPERGILLOSIS.

Invasive pulmonary aspergillosis (IPA) is a severe infection caused by Aspergillus species (Latgé, 1999) and affects primarily warm-blooded animals and as well as immunocompromised humans. Due to the success of immunosuppressive therapies in modern medicine has this disease had a steadily rising incidence during the last decades (McNeil et al., 2001). IPA is characterized by high mortality rates that may reach up to 90% depending on the host’s immune status (Singh and Paterson, 2005; Del Bono et al., 2008; Mikulka et al., 2009). Reasons for this are poor diagnostic means, the inefficiency of current antymycotic regimens (Baddley et al., 2010), and the general severity of the underlying diseases with their consequential risk factors. Among all Aspergillus Fungi AS OPPORTUNISTIC PATHOGENS

Pathogenic fungi have been classified historically in two major subgroups: primary and opportunistic ones (van Burik and Magi, 2003). While the former embraces fungi such as Coccidioides immitis or Histoplasma capsulatum that are capable of infecting a healthy host to cause severe systemic diseases, rely opportunistic fungi on an impaired host immune system to establish infection. Environmental saprobes, such as Aspergillus fumigatus or Cryptococcus neoformans are prominent examples from this group and rarely cause disease in a healthy individual. However, the number of associated clinical cases has significantly increased over the last decades, mainly based on modern medicine practices multiplying the number of immunosuppressed, susceptible individuals. Opportunistic fungi usually cannot thrive within the tissue of an immunocompetent individual. This suggests that they do not possess defined and unique characteristics to cause disease, features that have classically been coined as virulence factors (Casadevall and Pirofski, 1999). In fact, virulence of the two major fungal pathogens that are responsible for the majority of opportunistic infections, Candida albicans and A. fumigatus, appears to be multifactorial (Cassler, 1991; Latgé, 2001; Huber, 2004; Abad et al., 2010). This hampers the identification of specific targets against which chemotherapeutic compounds may be active. And indeed, current antifungal chemotherapy, which is mainly based on disrupting the integrity of the fungal cell membrane or wall (Hoehamer et al., 2010), is not satisfactory efficient. It has become evident that nutritional versatility, uptake systems, and metabolic pathways employed by opportunistic fungi during infection represent fundamental aspects of their pathogenicity. Albeit considered as unspecific virulence determinants, such aspects may constitute novel targets for antifungal therapy. For instance, iron acquisition from host tissues has been proven to be important for virulence of several pathogens, among them fungi as C. neoformans, C. albicans, or A. fumigatus (Ramaman and Wang, 2000; Jung et al., 2008; Haas, 2012). In the latter, in vivo iron acquisition was shown to be dependent on the siderophore system and independent of the iron reductive assimilation pathway (Schmitt et al., 2004), establishing this process as a virulence attribute. This exemplifies how a deeper knowledge of the metabolic status and nutrient acquisition strategies within infected tissues sheds light on fungal virulence mechanisms to assist in identifying novel targets of antifungal therapy (Brock, 2009).

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species, *A. fumigatus* accounts for approximately 90% of all cases of aspergillosis (Brakhage and Langfelder, 2002). Publication of its genome sequence (Nierman et al., 2005) prompted researchers to look for relevant characteristics and specific genes that could explain this prominent virulence capacity. However, comparative genome analyses failed to identify such specific virulence factors (Tikka and Latgé, 2005).

It has become more evident that its metabolic versatility enables *A. fumigatus* to thrive within the surrounding, infected tissues (Rhodes, 2006). In the course of pulmonary infection, *A. fumigatus* exploits the lung as principal metabolic environment and source of nutrients (Figure 1). In this respect, two major aspects are of special interest to understand the ability of this fungal pathogen to propagate in such a challenging environment: (i) the metabolic status of the fungus in vivo and regulatory cascades, metabolic processes, and stress responses that the fungus depends on within the surrounding tissue matrix, and (ii) the nutritional sources that the fungus exploits within such a highly specific growth medium, limiting nutrients, and the fungal anabolism. The following sections of this mini review will briefly summarize the current knowledge on nutrient acquisition and metabolic adaptation of *A. fumigatus* during invasive aspergillosis. Furthermore, it will outline approaches to overcome the negative consequences resulting from the pronounced redundancy of gene functions expressed by *A. fumigatus*, which complicates identification of novel antifungal drug targets.

### ADAPTING TO THE HOST

In its natural environment, the soil, *A. fumigatus* represents a prime saprobe that is characterized by its metabolic versatility and great adaptability. It has been suggested that such a competitive environment has evolved as a virulence strategy for this fungal pathogen (Askew, 2008; Fuller et al., 2011). This implies that *A. fumigatus* expresses distinct features supporting growth in human tissues based on adaptation to the adverse and variable conditions commonly encountered in the wild. Among these, its pronounced resistance to stressful conditions has to be taken into account. Reflecting elevated temperatures present in human tissues based on adaptation to the adverse and variable conditions commonly encountered in the wild. Among these, its pronounced resistance to stressful conditions has to be taken into account. Reflecting elevated temperatures present in host tissues, *A. fumigatus* displays an exquisite thermotolerance of up to 78°C (Bhabhra and Askew, 2005). Moreover, it is well adapted to grow at 37°C, the actual body temperature of humans, which represents an essential characteristic for pathogenicity. As a further example, hypoxia, which is commonly developed within compost piles (Wang et al., 2007), also develops during IPA in mice (Grahl et al., 2011) and, accordingly, *A. fumigatus*’ adaptation to hypoxic conditions is crucial for virulence (Willger et al., 2008).

In agreement with the importance of adaptation to the host, several stress response pathways and signal transduction cascades of *A. fumigatus* have been functionally characterized and their contributions to virulence were assessed (see review by Hartmann et al., 2011a). In essence, conditions of thermal stress, alkaline pH, hypoxia, iron depletion, and nitrogen starvation are encountered by the fungal pathogen when infecting a susceptible host. The ladder aspect became evidently clear from in vivo transcriptional profiling data that monitored the host adaptation process of *A. fumigatus* during early infection of neutropenic mice (McDonagh et al., 2008). By now, several additional profiling studies have sharpened our view on the transcriptional status of *A. fumigatus* under various environmental conditions that are relevant for pathogenesis, such as when feeding from proteinaceous substrates (Hartmann et al., 2011b), or when facing distinct stressors such as hypoxia or reactive oxidative species (McDonagh et al., 2008; Willger et al., 2008). The insights gained from such studies are instructive to identify cellular functions that are of relevance during infection and therefore assist in antifungal target identification. Validation of such promising candidates is commonly performed by approaches of reverse genetics: attenuated virulence may therefore be identified by various experimental approaches, such as elimination of a regulatory protein acting on expression of extracellular enzymes (transcription factor targeting), deletion of a set of genes encoding redundant cellular activities (gene family targeting), or by conditional expression of candidate genes to test for essentiality (conditional promoter replacement). The latter approach has to be considered as most straightforward and promising, given the vast redundancy among proteins expressed by *A. fumigatus* to support its saprobic lifestyle.

### TARGETING TRANSCRIPTIONAL REGULATORS

Transcription factors are fundamental for adapting to changing conditions by modifying gene expression patterns. Consequently,
COPING WITH GENETIC REDUNDANCY

Insights from recent studies on A. fumigatus virulence yielded the fundamental conclusion that this aspergillus is well-equipped to sustain its nutritional supply in the host. However, the osmotic stress that this saprobe is subjected to during the pathogenic lifestyle of A. fumigatus, i.e., extracellular digestion of complex substrates and proteins through the action of extracellular proteases, impedes a comprehensive analysis. Nonetheless, in this study, we demonstrate that the Aspergillus genome was achieved in a recombinant murine infection model or that redundant factors take over from the deleted ones.

BIOSYNTHETIC ROUTES AND ESSENTIAL GENES AS PRIMARY TARGETS

The metabolic versatility displayed by A. fumigatus supports its growth and therefore virulence inside a susceptible host. Despite this ignorance, several anabolic genes with their respective products have been identified to be essential for growth for the primary targets.

gene family from the A. fumigatus genome was achieved in a pivotal study with the aim to investigate any supportive role of oligopeptide transport in pathogenesis. The resulting octuple mutant did, however, not display any differences in virulence in comparison to its wild-type progenitor. Even interfering with extracellular proteolysis of this strain by additionally deleting the pyrG gene did not alter its virulence capacities, again highlighting the pronounced degree of redundancy encoded by the A. fumigatus genome. However, this study proves that such approaches facilitate identification of relevant antifungal drug targets that are based on gene family products.

Insights from recent studies on A. fumigatus virulence yielded the fundamental conclusion that this aspergillus is well-equipped to sustain its nutritional supply in the host. However, the osmotic stress that this saprobe is subjected to during the pathogenic lifestyle of A. fumigatus, i.e., extracellular digestion of complex substrates and proteins through the action of extracellular proteases, impedes a comprehensive analysis. Nonetheless, in this study, we demonstrate that the Aspergillus genome was achieved in a recombinant murine infection model or that redundant factors take over from the deleted ones.
In a further development of deleting biosynthetic genes to generate auxotroph strains, pathways that are required for growth under any condition tested, and that are therefore generally essential, represent an attractive option to be selected as targets for antifungal therapy. Since the functions of the corresponding proteins are fundamental for fungal growth, their impairment would consequently eliminate virulence. An elegant approach for essential gene identification was validated by Romero et al. (2003) who developed a conditional promoter replacement (CPR) strategy further by employing the nitrogen-regulated A. fumigatus mini A promoter (pNiA; Romero et al., 2003; Hu et al., 2007). In this setup, expression of the gene of interest is blocked in the presence of ammonium, whereas nitrate as N-source allows proper expression of the gene under pNiA control. The power of this system was demonstrated by the close phenotypic correlation between pNiA-CPR strains under repressing conditions with respective disruption mutants. Furthermore, such conditional strains could be directly tested for virulence in animal models, although being limited to systemic infections. In fact, 35 essential genes out of an initial screening pool comprising 54 candidates were identified in this seminal study, which may now be subjected to further analysis. Therefore, the CPR approach represents a valid and most straight-forward method for large scale essential gene identification.

NOVEL TOOLS PROVIDE PROMISING PERSPECTIVES

The most promising strategy for drug target prioritization to fight aspergillosis lies in the identification of non-redundant and essential gene products. As future trend emerging from distinct candidate approaches, comprehensive, large scale screening studies are reasonably required. These could include the generation of a collection of defined deletion mutants, comprising every single gene annotated from a refined A. fumigatus genome sequence. Including conditional alleles would further scrutinize essential cellular functions that are based on single gene products and appears as a superior strategy. In particular, recent developments that demonstrated the feasibility of doxycycline-dependent expression modules in Aspergillus (Voigt et al., 2005; Meyer et al., 2011; Dichtl et al., 2012) pave the road for such advanced CPR strategies that might even allow for virulence tests in pulmonary aspergillosis models. As an alternative to extensive and randomized screening, network approaches of systems biology might serve as more efficient and straight-forward tactic (Chavali et al., 2012; Horn et al., 2012). In conjunction, new molecular tools for multiple gene targeting will allow comprehensive understanding of the in vivo A. fumigatus metabolic status. Concluding, the advanced molecular biology of A. fumigatus (Krappmann, 2006) holds the future promise of innovative strategies for antifungal drug target identification, an urgent task in fighting against this first mold pathogen in Europe (Senior, 2009).

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