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Virulence factors in fungal pathogens of man

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Human fungal pathogens are a commonly underestimated cause of severe diseases associated with high morbidity and mortality. Like other pathogens, their survival and growth in the host, as well as subsequent host damage, is thought to be mediated by virulence factors which set them apart from harmless microbes. In this review, we describe and discuss commonly employed strategies for fungal survival and growth in the host and how these affect the host–fungus interactions to lead to disease. While many of these strategies require host-specific virulence factors, more generally any fitness factor which allows growth under host-like conditions can be required for pathogenesis.Furthermore, we briefly summarize how different fungal pathogens are thought to damage the host. We find that in addition to a core of common activities relevant for growth, different groups of fungi employ different strategies which in spite of (or together with) the host's response can lead to disease.

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Introduction

Interactions of microbes with plants, animals and humans include symbiotic, commensal and parasitic relationships, where the latter can result in disease of the host. Such infectious diseases are characterized by host damage, the degree of which is generally used to define the virulence of the microbe. This review will focus on human fungal pathogens and their attributes associated with disease.

Fungal pathogens

The fungal world is very diverse, including an estimated 3–6 million fungal species [1,2]. Of these, only very few (about 150–300) are known to cause disease in humans [3,4]. Still, fungal infections are not rare, although they predominantly affect immunocompromised individuals. However, even individuals with severe immunodeficiencies are not 'living petri dishes' in the sense that they can be infected by any fungus. Thus, it is commonly believed that *bona fide* human pathogenic fungi must have obtained distinct characteristics which make them pathogenic.

Infecting fungi come from two different sources: the environment and distinct host niches. Environmental fungal pathogens enter human hosts occasionally and often accidentally to cause disease. In the environment, such fungi are likely at least intermittently exposed to micro-niches similar to the conditions in their human host. These exposures most likely result in evolutionary (pre-) adaptations with benefits during pathogenesis ('The environmental virulence school') [5]. In fact, the majority of human fungal pathogens are of environmental origin, including *Cryptococcus*, *Histoplasma*, *Blastomyces* or *Aspergillus* species.

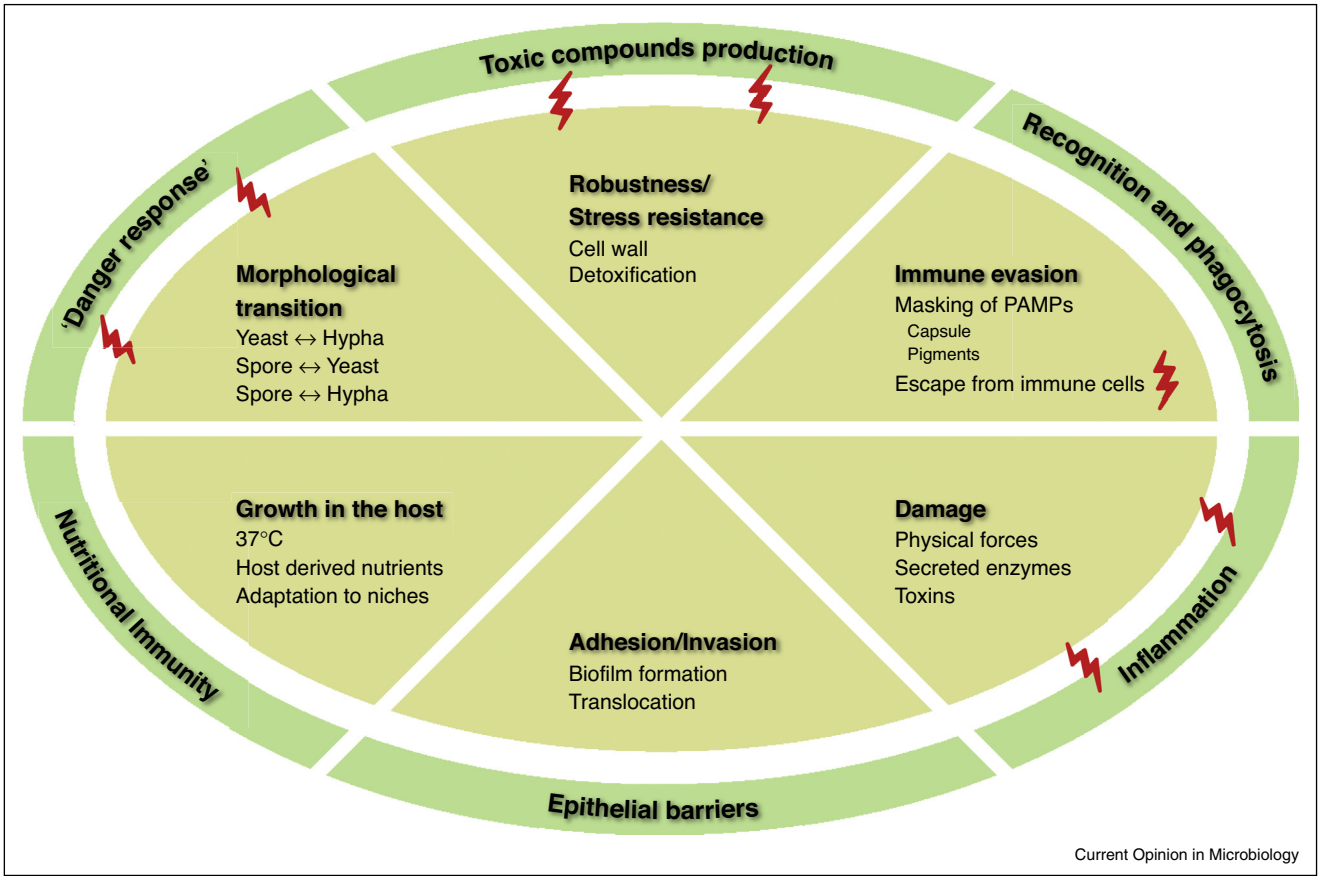
The other group, human host-associated fungal pathogens, can be further subdivided. First, the almost obligatory human pathogens (the anthrophilic dermatophytes), which can infect even fully immunocompetent individuals, and which can be readily transferred between humans. Second, commensal fungal pathogens like *Candida albicans*, which are normally harmless members of the host's microbiome, and only cause disease under facilitating circumstances. These commensal opportunistic pathogens are apparently well adapted to their niches in the human host. Adaptations due to occasional and transient exposures to the immune system during commensalism could feasibly 'train' these fungi to counteract immune responses in their pathogenic phases ('The commensal virulence school') [6].

Virulence factors: attributes required for survival, replication, and damage

Two processes are required for pathogenesis: (a) survival and growth of the infecting microorganism and (b) damage of the host, a disruption of homeostasis manifested as disease symptoms.

Survival of pathogens within the generally hostile host is essential for initial establishment of an infection. Attributes required for this survival and later replication can be of a general nature (e.g. metabolism of nutrients) or specific to human or mammalian hosts (e.g. immune evasion factors) (Figure 1). Still, even among microbes

Figure 1



Virulence attributes of a prototypic human pathogenic fungus in interaction with the host. Host damage and disease result from the interplay between fungal fitness and virulence factors (central ovoid) and host responses (outer ring). Potential damage-causing interactions are highlighted in red.

which permanently live in association with a host, like the human microbiome, few are able to become pathogenic, that is, to enter host–pathogen relationships which ultimately damage the host. Additional microbial attributes, which are often termed 'virulence factors', are required to this end. These factors, which can directly cause damage, are found in pathogenic viruses, bacteria, parasites and fungi, and often share striking similarities in their modes of action and regulation patterns.

However, it is important to stress that the ability to cause damage is not a property of the microorganism alone, but rather emerges from the interplay of a susceptible host and a microbe in the damage-response framework [7,8]. Inappropriate or unbalanced host responses, both, too low or too high, can lead to damage: for instance, local inflammation can attract neutrophils and their lethal weaponry, which will not only kill the microbes, but also cause tissue damage. In an ultimate form of immune overreaction, a local inflammation may result in a systemic cytokine storm and finally sepsis, one of the major causes of mortality in the Western world [9].

The two different aspects of pathogenicity (survival and growth of microbes and damage of the host) are reflected by commonly used read-outs to judge virulence: viable cell number within organs, histology, clinical symptoms such as fever or body weight loss, organ damage, host immune response, and finally death of the host. Here, we describe the common factors and strategies of pathogenic fungi which allow for one or both of these aspects to be realized.

Growth in the host

Growth is a characteristic, but not always essential during a pathogen's life. Transient non-replicative (dormant) phases can be advantageous, for example, in the form of biofilms or granuloma-like structures, which can favor microbial persistence [10,11] as there is a general tendency for slow or no growth associated with antibiotic and biocide resistance [12].

The ability to in fact grow in the human host requires metabolic activity at 37 °C and the ability to take up and metabolize host-derived nutrients [13•]. Interestingly, some metabolic pathways are crucial for fungal growth

in the host, but not required in rich standard laboratory media; for example the glyoxylate cycle or the methylcitrate cycle [14–16]. These can hence be considered associated with and essential for virulence. Because of their relative host-specificity, these pathways may not be detected in conventional screens for drug targets performed in rich media, and thus have a great potential to include novel targets.

Furthermore, some nutrients must be actively abstracted from host molecules, for example, nitrogen from host proteins by secreted protease activities [17]. Of particular relevance for fungal pathogens is the acquisition of micronutrients such as metals, since the host has evolved mechanisms to deny access to metals like zinc or iron (known as 'nutritional immunity') [18]. In turn, fungal pathogens have developed sophisticated strategies to gain iron, zinc and other metals from the host [19•,20,21]. Similarly, to survive in the host fungal pathogens must exhibit physical robustness (e.g. conferred by a protective cell wall [22]) and stress resistance (e.g. against reactive oxygen species (ROS) [23]) or must be able to manipulate environmental conditions like the ambient pH [14]. The latter can, for example, be achieved by active environmental alkalinization [24,25].

Immune evasion strategies

Strategies to avoid, counteract or escape immune responses can be evidently observed only in the context of a host. To avoid recognition, mechanisms to conceal immunogenic surface structures (Pathogen Associated Molecular Pattern – PAMPs) exist, for example, by modifying them or covering them with capsules or even host-derived molecules [26•,27,28]. Antimicrobial substances such as ROS, antimicrobial peptides (AMPs), complement factors or antibodies can further more be degraded by fungal pathogens (e.g. see [29]). Pigments are common to protect fungi against many immune defense mechanisms and even antimycotics [30]. A hallmark of the innate immunity is phagocytosis, and pathogens regularly exposed to host phagocytes or phagocyte-like cells (e.g. amoebae in the environment, see above) have often developed sophisticated mechanisms to escape by membrane penetration, host cell lysis or expulsion [31]. Fungi that stay inside the phagosome are often known to alter their phagosomal compartment to allow intracellular survival [32,33,34•].

Adhesion and invasion factors

Adhesins — proteins (or other molecules) which mediate attachment to host cells — are nearly universally found in pathogenic microbes. While commensal microbes predominantly reside within the mucus in distance to AMP-producing epithelial cells, pathogens generally directly bind to host cells. This avoids getting flushed away from mucosal surfaces, and provides the intimate contact required to manipulate and invade host cells.

Invasion into host cells and tissues is often described as one of the defining activities of pathogenic microbes [35], although some symbiotic microbes are known to also invade host cells [36]. While bacteria almost always invade host cells by triggering their up-take through invasin-host receptor binding (induced endocytosis), parasites and fungi can often drive invasion by their own activities like filamentous growth or turgor pressure increase (active penetration) [37]. Some fungi are known to use both invasion strategies [38]. Translocation into deeper tissue, however, does not always require cellular invasion. For example, the pathogen may invade via disrupted interepithelial connections or through necrotic host cells, possible strategies which are being considered for some fungal pathogens. Furthermore, pathogenic fungi like *Cryptococcus neoformans* use host cells such as macrophages as vehicles to overcome host barriers, known as 'Trojan horse' strategy [39].

Host manipulation and exploitation by effectors

Host manipulation by effector proteins is a common theme in pathogenic microbes. These proteins specifically interact with host molecules to manipulate the host cell in favor of the pathogen. In a broader definition of 'effectors', this may include invasins which induce endocytosis by triggering receptor-mediated host cytoskeleton rearrangements (see above) [40]. However, more commonly the term 'effector' is used for proteins which cross the host cell membrane and manipulate intracellular processes. These effectors are common in bacteria and plant pathogenic fungi and often modulate host cell metabolism to suit the pathogen (e.g. metabolic priming by the plant pathogen *Ustilago maydis*) [41]. Crossing the host membrane is essential for the action of these effectors. This is frequently accomplished by specialized secretion systems in pathogenic bacteria, but in plant pathogenic fungi the mechanisms are not clear yet. Surprisingly, so far not a single intracellular effector protein has been described in human pathogenic fungi.

Direct host damage

Pathogenic fungi can directly cause damage to host cells by physical forces during host cell invasion or escape, as well as by secreted factors. Such factors can comprise hydrolytic enzymes (e.g. proteases or lipases) or lytic toxins in the form of peptides or small metabolites [30]. In fact, toxins which cause pathology and disease even in the absence of live microbes are considered classical virulence factors especially in bacteria. Toxic secondary metabolites are common especially in molds. Only recently, the first peptide toxin has been identified in a human pathogenic fungus, the yeast *C. albicans* [42].

Morphology and virulence programs

Certain environmental pathogens can recognize typical host-associated conditions and respond by initiating defined virulence programs. For example, many dimorphic

fungal pathogens switch their morphology and its associated gene expression profile in response to mammalian body temperature [43]. Other host-related signals, such as contact to epithelial cells, can similarly trigger morphological and transcriptome changes in commensal fungal pathogens. This 'adaptive prediction' pattern [44] is thought to help the pathogen to prepare for upcoming, possibly hostile conditions in the host. On the other side, the host is also able to discriminate between 'harmless' and 'pathogenic' morphological forms and to detect a high fungal burden. These signals elicit a 'danger response' of the host in an interesting example of reciprocal interspecies communication [45].

Examples of fungal virulence factors

Pathogenic fungi employ very different combinations of the virulence strategies discussed above. The specific repertoire of any given species is often defined by the environment it or its ancestors inhabited before becoming pathogenic [46]. Much can be learned from the common themes and the specific exceptions in single species. In this section, we will therefore discuss specific factors and attributes characteristic for the most common species of endogenous and environmental fungal pathogens.

Endogenous pathogenic fungi

Candida albicans *and non-albicans* ***Candida*** *species*

C. albicans is a member of the normal human microbiome, but can cause infections that range from superficial to life-threatening systemic. Key virulence attributes are its broad metabolic flexibility [13•] and a yeast-to-hypha dimorphic transition together with a hyphae-associated genetic program. The latter comprises the expression of genes which allow adhesion, thigmotropism, active and induced invasion, (micro)nutrient acquisition, direct host cell damage, biofilm formation, and diverse types of immune evasion [34•,47•].

Although less frequent than *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei* and *C. dubliniensis* are associated with human disease [48]. *C. glabrata* is a successful pathogen despite lacking true hyphae. Its high intrinsic stress resistance and immune evasion are considered important virulence attributes. In addition, *C. glabrata* is auxotrophic for thiamine, pyridoxine, and nicotinic acid, allowing the latter to serve as a host-derived signal for this fungus [49–51].

Dermatophytes and ***Malassezia***

Dermatophytes include species of the genera *Microsporum*, *Epydermophyton*, and *Trichophyton*, all of which share a tropism for skin, hair and nails. Their main virulence factors include adherence and growth on keratinized tissue, which rely on secreted hydrolytic enzymes such as proteases, phospholipases, and lipases. Secretion of sulfite allows coping with increased levels of cysteine as a result of keratin degradation [52]. In addition, dermatophytes are known to secrete molecules which increase tissue damage [53].

Malassezia comprise lipodependent, dimorphic yeasts of the human skin [54], which are associated with seborrheic dermatitis, pityriasis versicolor, and dandruff [55•]. All *Malassezia* species have lost their fatty acid synthase [54] and instead acquire host lipids via secreted lipases. Indolic compounds derived from host tryptophan allow protective pigment synthesis [56] and extensive immune modulation [57].

Environmental pathogenic fungi

Aspergillus fumigatus

A. fumigatus, a saprophytic soil fungus which is able to grow at high temperatures, is the major cause of invasive aspergillosis in immunocompromised individuals [58]. A hydrophobic outer rodlet layer prevents immune recognition of inhaled conidia, while conidial melanin masks immunostimulatory glucans and protects against ROS and killing by immune cells. Conidial germination, hyphal growth and production of siderophores are essential for full virulence. In addition, *A. fumigatus* readily secretes secondary metabolites like the immunosuppressive gliotoxin during infection. Peptidases, proteases and ROS detoxifying enzymes likely contribute to its virulence [59,60].

Cryptococcus neoformans and C. gattii

The causative agents of cryptococcosis, *C. neoformans* and *C. gattii*, are facultative intracellular yeasts. A characteristic and one of the main virulence factors of this species complex is the production of an extensive capsule. This down-regulates cytokine production by immune cells, sequesters complement components and reduces the antigen-presenting ability of monocytes. The capsule can serve to 'hide' the fungus from recognition by phagocytes, thus avoiding phagocytosis [61]. Other important virulence factors include the production of melanin (protecting the fungus from oxidative and other stresses), the ability to grow at 37 °C, and the secretion of extracellular enzymes [62•].

Histoplasma capsulatum and Blastomyces dermatitidis

H. capsulatum and *B. dermatitidis* are dimorphic fungi that shift from environmental molds to pathogenic yeasts when their spores are inhaled. Interestingly, in both species a histidine kinase controls this shift as well as cell wall integrity, sporulation and virulence. Yeast-specific virulence factors include calcium-binding proteins — implicated in macrophage survival and pulmonary infection in *H. capsulatum*, and in dysregulating host cytokine production in *B. dermatitidis* [63]. Decreased β-1,3-glucan and increased α-1,3-glucan cell wall levels upon hyphal-to-yeast transition contribute to immune evasion. Further virulence traits are siderophore production, detoxification

or suppression of reactive oxygen and nitrogen species, and intracellular replication in macrophages [43].

Pneumocystis jiroveci

P. jirovecii causes asymptomatic or mild infection in healthy humans, but severe pneumonia in immunocompromised patients [64]. Identification of virulence factors has so far been hampered by the lack of *in vitro* culture systems. However, high-frequency antigenic variation by selective expression of the major surface glycoprotein gene family likely promotes immune avoidance and survival in the lung [65].

Mucorales

Infections with mucorales have a high mortality even under clinical treatment [66,67]. The causes for this high virulence are not well investigated yet, but iron uptake from bacterial xenosiderophores and (most likely) host hemoglobin seem to play important roles [68,69•]. This and adhesion to extracellular matrix proteins may explain their angioinvasion, leading to dissemination, thrombosis, and necrosis [67].

Conclusion

For a pathogenic fungus, as for any other human pathogen, the human body presents an environment in which it needs to survive and ultimately, grow. The traits required for survival and growth in this specific environment are usually considered virulence factors. A clear-cut definition of virulence factors is, however, difficult, as many traits are 'dual use', having important functions both during pathogenesis and in the environment or during benign growth phases: heat resistance can protect against the mammalian body temperature as well as against heat generated in decaying compost piles; phagocyte escape mechanisms are good against macrophages and amoebae. Hence, exclusively host-specific factors are likely rare or non-existent, and in a broader sense, a virulence factor is a survival trait realized in a (susceptible) host. Resulting from their direct action and from the host's response, these factors lead to the disruption of host homeostasis and hence, disease.

While many of these survival traits are shared among human fungal pathogens, their exact combination in any given species strongly depends on their evolutionary history. The examples above show how different fungi are equipped to deal with the host environment. Especially the common survival strategies, including the general metabolic pathways of these fungi, may provide good opportunities to reduce the fungal fitness in the host, and thus help to clear fungal infections.

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