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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.

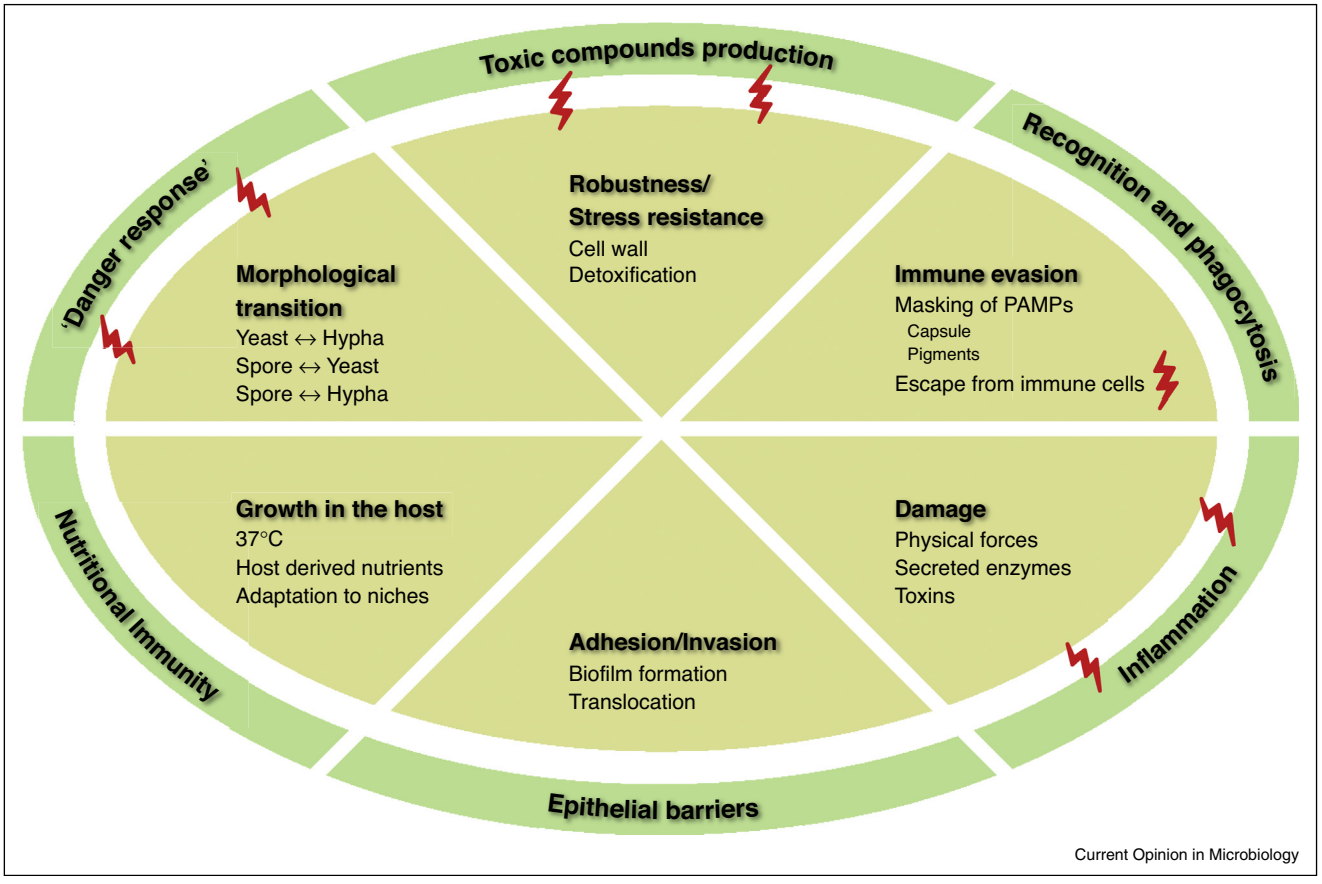
The other group, human host-associated fungal pathogens, can be further subdivided. First, the almost obligatory human pathogens (the anthrophilic dermatophytes), which can infect even fully immunocompetent individuals, and which can be readily transferred between humans. Second, commensal fungal pathogens 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