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A REVIEW OF THE VIRULENCE FACTORS OF PATHOGENIC FUNGI

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SUMMARY

Fungal infections are becoming more prevalent especially with increase in immunodeficiency disorders, immunosuppression following transplantation, cancers and cancer treatment. They are ubiquitous and cause infections which may be trivial or more deep seated and severe infections associated with mortality. The ability of some fungal species to cause disease is due to various virulence factors which help with fungal survival and persistence in the host resulting in tissue damage and disease. This review discusses these virulence factors. These factors include an ability to adhere to hosts' tissues, production of enzymes that cause tissue damage and direct interference with host defences. Pathogenic fungi produce catalases and Mannitol which protect against reactive oxygen species (ROS). Some fungi notably, dimorphic fungi and *C. albicans* have the ability to switch from one form to another. Thermotolerance, at least to 37^{0}C, is critical for survival in mammalian host and contributes to dissemination. Melanin is produced by a number of pathogenic fungi, and protects against harsh conditions such as UV radiation, increased temperature and ROS. The ability to obtain Iron (Fe) from the storage or transport forms in the host is also a virulence factor and calcineurin acts as a sensor for pathogenic fungi.

Key words: Fungi, virulence, pathogenic, infections, dimorphism, thermotolerance

UNE REVUE DES FACTEURS DE VIRULENCE DES CHAMPIGNONS PATHOGENES

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RESUME

Les infections fongiques sont de plus en plus fréquentes, en particulier avec l'augmentation des troubles de l'immunodéficience, l'immunosuppression après la transplantation, les cancers et le traitement du cancer. Ils sont ubiquitaires et provoquent des infections qui peuvent êtretriviales ou plus profondes et des infections graves associées à la mortalité. La capacité de certaines espèces fongiques à provoquer une maladie est due à divers facteurs de virulence qui aident à la survie des champignons et la persistance dans l'hôterésultant dans les dommages des tissus et la maladie. Cette revue traite ces facteurs de virulence. Ces facteurs comprennent une capacité à adhérer aux hôtes, la production d'enzymes qui causent des dommages des tissus et une interférence directe avec les défenses de l'hôte. Pathogènes produisent des catalases du Mannitol qui protègent contre les espècesréactives de l'oxygène. Certains champignons notamment les champignons dimorphes et C. albicans ont la capacité de passer d'une forme à l'autre. La thermo tolérance, au moins 370C, est essentielle pour la survie chez un hôtemammifère et contribue à la diffusion. La mélanine est produite par un certain nombre de champignons pathogènes, et protège contre les conditions difficiles telles que le rayonnement UV, la températureaugmentée et ROS. La capacité d'obtenir du Fe à partir des formes de stockage ou de transport dans l'hôte est également un facteur de virulence et la calcineurine agit en tant que capteur pour les champignons pathogènes.

Mots clés: Champignons, virulence, pathogène, infections, thermotolérance dimorphe.

1. INTRODUCTION

Fungal infections have become very prevalent with associated increase in mortality and morbidity. This is especially so for life-threatening invasive fungal infections as a result of increase in immunodeficiency disorders such acquired immune deficiency syndrome (AIDS), cancer and cancer treatment, and immunosuppressive therapy following transplantation. Fungi are ubiquitous, they cause infections when the spores are inhaled, e.g. *Aspergillus fumigatus*; by direct skin contact or implantation e.g. *Trichophytonrubrum*, or by commensals when there are changes in the host's normal flora or breech in mucosal barrier as seen with *Candida albicans*. However, for most immunocompetent

individuals, immune mechanisms are able to control and contain these fungal infections.

Fungi cause different disease types; the very common superficial infections, e.g. ring- worm or onychomycosis caused by the dermatophytes- *T.rubrum*, invasive or deep- seated severe infections such as meningitis or pneumonia caused by *C. immitis*or *C. neoformans*and allergic diseases in atopic hosts, e.g. allergic bronchopulmonary aspergillosis caused by *A. fumigatus*. While mucocutaneous infections may be seen in immunocompetent individuals, invasive opportunistic infections occur in the immunosuppressed.

The ability of some fungal species to cause disease is due to various virulence factors which help with fungal survival and persistence in the host resulting in tissue damage and disease. These factors include an ability to adhere to hosts' tissues, production of enzymes that cause tissue damage and direct interference with host defences. Some fungi, notably dimorphic fungi and *C. albicans* have the ability to switch from one form to another (1). Thermotolerance, at least to 37^0C, is critical for survival in mammalian host and contributes to dissemination (2).

2. PATHOGENIC FUNGI OF MEDICAL IMPORTANCE

Fungi are eukaryotes that propagate by the production of spores. Most fungi can reproduce both sexually and asexually, and are ubiquitous in the environment. There are three major phyla of fungi to which most of the human pathogenic fungi belong. These are the Ascomycota, Basidiomycota, and Zygomycota.

Ascomycota

The fungi that belong to this group are known as sac fungi (ascus), and are so named because they reproduce sexually by means of ascospores. Sexual reproduction involves the formation of new cells from the fusion of hyphae, this new cell divides to form the ascospores within the ascus. They also reproduce asexually by budding of their conidia which are asexual spores. Asexual reproduction occurs in favourable conditions. Examples of pathogenic fungi in this phyla are dermatophytes, (Microsporum, Trichophyton, and Epidermophyton) dimorphic fungi (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Candida spp*, *Paracocidioides brasiliensis*,and *Coccidioides immitis*) and septate filamentous fungi (*Aspergillus spp*).

Zygomycota

Zygomycetes reproduce sexually by the production of zygospores, and asexually by sporangiospores. They form broad aseptate hyphae with fast growing colonies. The fungi in this group are usually contaminants, but they are known to also cause invasive diseases. Examples include Mucorspp, Rhizopusoryzae, and Rhizomucor spp.

Basidiomycota

The fungi in this group are known as club fungi because they produce sexual spores with a club shaped structure. The sexual spores are known as basidiospores. They reproduce sexually and asexually. They are found in aquatic and terrestrial habitats, and also form ballistospores which are discharged forcefully into the air. Examples of pathogenic forms are *Cryptococcus spp*, *Malasseziaspp,* and Trichosporon.

3. VIRULENCE FACTORS OF PATHOGENIC FUNGI

There are thought to be about 1.5 million species of fungi on earth, but only about 600 are pathogenic to man, with about 30 commonly implicated in human disease. Fungal diseases are generally known as mycoses. The ability of fungi to cause disease and their virulence factors are borne out of strategies to overcome and survive in the harsh environment of the host. Primary pathogens cause disease in immunocompetent hosts; they are ubiquitous and on inhalation of their conidia in large doses, may convert to pathogenic forms causing disease. Examples are *C. immitis*, *H. capsulatum*, *B. dermatitidis*, and *P.* brasiliensis. Opportunistic pathogens may be commensals like C. albicans or saprophytes such as *A. fumigatus*and *C. neoformans*. They cause disease in immunocompromised persons. This distinction however, is not clear cut, as primary pathogens such as *C. immitis*may cause virulent disease in immunocompromised persons and *C. neoformans*may occasionally cause disease in immunocompetent persons.

Adhesins

Pathogenic fungi are able to cause disease by a number of virulence factors. These factors include structures that enable them to adhere to tissues so as to avoid being cleared or swept away by ciliary movement or mucous. *C. albicans*as an example is known to have a number of adhesion molecules. *C.albicans* is able to bind to medical devices forming a biofilm which enhances its pathogenicity (3). The adhesion molecules include Als proteins, Hwp1p, Eap1p, Cshlp and others (4). There are eight genes that code for Als proteins, these proteins mediate adhesion to collagen, laminin, endothelial cells, epithelial cells and cell-to-cell aggregation (5). Hwp1p mediates binding to epithelium while Int1p mediates adhesion to platelets (6). Abrogation of Als3 is the basis for the development of a vaccine to prevent invasive candidiasis (7).

Other examples of pathogenic fungi with adhesion molecules include *A. fumigatus*, *H. capsulatum*and *P. brasiliensis*. Conidia of *A.fumigatus* are covered with hydrophobic proteins known as rodlets. These rodlet proteins are encoded for by RODA and RODB genes and, mediate adhesion of the conidia to albumin and collagen. Receptors on the surface of hyphae include galactomannan and chitin of *A. fumigatus*which mediate adhesion to complement, fibrinogen, immunoglobulin, and surfactant A and D (8). Blastomyces adheres via BAD 1 which binds CR3 and CD14 on phagocytes and also modulates host immune responses (9). *H. capsulatum*uses HSP60 (10), while *P.*

*brasiliensis*uses glyceraldehydes 3-phosphate dehydrogenase (GAPDH) and polypeptides p19, p30, p32 (11), and Coccidioides uses its spherule outer wall (SOW) for adhesion (12).

Dimorphism and Thermotolerance

Another way pathogenic fungi become virulent is by morphogenesis. Most pathogenic fungi exhibit dimorphism, that is, they can switch from one form which is not pathogenic to a pathogenic form. While they exist as one morphotype in the environment or as commensals, they exist as another morphotype when they cause infection. Dimorphic fungi include *B. dermatitidis*, *C. immitis*, *H. capsulatum, P brasiliensis, and C. albicans*. They exist as yeast or moulds; yeasts are round or ovoid unicellular organisms. It reproduces by binary fission to yield a separate, independent daughter cell. Moulds on the other hand are filamentous, they grow by apical extension forming cellular units which are separated by septates but still attached to the mould. These branching cellular units are known as hyphae or mycelium. Some fungi may have other morphotypes, for example, *C. immitis*may form large endosporulatingspherules. Intermediate forms such as pseudohyphae may exist as is seen in *C. albicans*

Ability to grow at elevated temperature is another virulence factor. Fungi that cause systemic infections are able to grow at body temperature and even at febrile temperatures of 38-42^{0}C. *A. fumigatus*isis particularly thermophilic, and can grow at temperatures of up to 55-77^{0}C (13). HSP 70 is thought to be required by fungi to adapt to high temperatures (14). Pathogenic fungi also change from one form to the other at different temperatures, while most fungi exist as mould at ambient temperature; they become yeast at the mammalian temperature which is the pathogenic form. When the transition from mycelia to yeast is blocked in *H. capsulatum*, the organism continued to grow at 37^0 C but was avirulent (15). For *C. albicans*, both forms are pathogenic and, it changes its form in response to changes in the environment existing as the unicellular yeast at lower temperature and acidic pH, which is spread in the environment. The hyphal form is used for tissue invasion (4).

Capsules

Capsulated fungi are usually pathogenic. *C. neoformans*coats itself with capsule (glucoronoxymannan) with which it resists phagocytosis. The Polysaccharide capsules are usually prominent in isolates causing infections while environmental *C. neoformans*isare weakly encapsulated. Acapsular strains are not virulent as they are easily phagocytosed. The genes responsible for encapsulation are CAP 59 and CAP 64 (16). Capsules also deplete complement and cause a dysregulation of the cytokine network. The capsule also inhibits the mobilisation of leucocytes to the site of infection (17)

Production of enzymes

Pathogenic fungi release degradative enzymes which enable them to establish disease and disseminate, these enzymes cause tissue damage in the host and impair host immune defences. *C. albicans*secretes extracellular phospholipases, lipases and proteases. Pathogenic candida secrete much more phospholipase than commensal strains, and phospholipases A, B, C and D act by breaking the ester bonds. These enzymes are also important for nutrition and Fe acquisition (6,18). *C. albicans*also secretes SAP (secreted aspartyl proteinases) which hydrolyse extracellular matrix proteins, coagulation factors such as Hageman factor and factor X, host defence proteins e.g. mucin, IgA andlactoferrin and complements (19).

*A. fumigatus*secretes proteases (serine and aspartic protease, metalloprotease) and phospholipases which degrade elastin present in lung tissue. The serine proteases degrade collagen, fibrin and fibrinogen (2). *C. neoformans*also secretes proteases and phospholipases, lysophospholipase and lysophospholipase-transacylase (LPTA). These enzymes destroy lung surfactant and enhance adhesion (20,21). In addition, *C. neoformans*is thought to invade the CNS by the production of urease (22). Urease production is also utilised by *Coccidioides*, increasing alkalinity at sites of infection and urease deficient strains cannot disseminate (23).

Defence against reactive oxygen and nitrogen species

Neutrophils and macrophages use oxidative mechanisms (ROS and RNS) to damage fungi by lipid peroxidation and nucleic acid breaks. Pathogenic fungi produce enzymes with which they can be protected from the effects of oxidation. They produce catalases for protection against ROS (24). *C. albicans* uses superoxide dismutase and HSP to protect against ROS (25), while*C. Neoformans* uses the production of copper, zinc and peroxidase to resist oxidation (26). *A. fumigatus*produces three catalases; Cat- A associated with conidia, and Cat 1p and Cat 2p associated with hyphae (8) as well as superoxide dismutases (containing Mn, Cu and Zn) that protects it from oxidative damage (27).

Melanin

Melanin is produced by a number of pathogenic fungi, it is hydrophobic and protects against harsh conditions such as UV radiation and increased temperature. It also protects against ROS (27). In *C. neoformans*, melanin has been shown to evade anti-fungal damage and inhibit antibody mediated phagocytosis (28). Melanin is also synthesised by *A. fumigatus*from acetate using a 6 genes pathway (8). *H. capsulatum, Blastomyces, P.brasiliensis* are other pathogenic fungi which produce melanin (23).

TABLE 1: VIRULENCE FACTORS OF SOME PATHOGENIC FUNGI

Fungal pathogen	Virulence factors	Role in pathogenicity	Ref
Aspergillus spp	Galactomannan,chitin,Rodlets	Adhesion.	8
	Proteases and phospholipases	Degradation of elastin in lung tissue and tissue damage.	2
	Catalases and SOD	Protection from oxidative damage.	8,27
	Melanin.	Protection from harsh conditions and oxidative damage.	8
	Fe-siderophores (Sid A gene)	Fe uptake for growth.	29
	Gliotoxin	Immunosuppression.	2
	Calcineurin CNAA gene	Growth of fungi and tissue invasion.	34
	Ability to grow at 37-420C	Survival in host tissues, ability to cause systemic infection.	13
Candida spp	Als, Hwp1p, Eap1p, Cshlp	Adhesion	4
	Dimorphism	Survival in host, tissue invasion and dissemination of disease.	4
	Phospholipases A, B, C, and D	Tissue damage and disease dissemination.	6,8,19
	Lipases and proteases (SAP SOD, HSP, catalases)	Protection from oxidative damage	25
	Siderophores, RBT5, Reductases	Fe uptake for growth and metabolism.	31,3
Cryptococcus spp	Capsule (CAP 59 and 64)	Resists phagocytosis.	16,1
	Lipases, phospholipases, lysophospholipase and LPTA.	Destroys lung surfactant and enhances adhesion.	20,2
	Urease		22
	Cu, Zn, peroxidase and mannitol	Invasion of the CNS. Protection from oxidative damage.	27,3
	Melanin	Protection from harsh condition inhibits phagocytosis and anti-fungal damage.	28 4
		Evasion of immune defences.	4
	Phenotypic switching	Survival and tissue invasion	4
	Calcineurin (CNA1 gene)	Fe acquisition	
	Reductases, cft1, cfo1		

Iron acquisition

Fe is needed by the fungi for growth, respiration and other metabolic processes, but is not available in the free form in the host. The ability therefore, to obtain Fe from the storage or transport forms in the host is a virulence factor. *A. fumigatus* uses three mechanisms of Fe uptake; reductase Fe uptake, siderophore-mediated Fe uptake and ferrous Fe uptake mechanisms (29).

Triacetylfusannine C (TAFC) and desferriferricrocin (DFFC) are two major siderophores identified for *A. nidulans* (30). *C.albicans* acquires iron by different mechanisms which include the use of siderophores, and by direct uptake from heme in red blood cells using haemoglobin receptors (RBT5 family) on their cell surface (31). *C. albicans* also employs a reductive mechanism using the reductases -Cfl1/Fre and Cfl95/Fre 10/Rbt 2 (32).

Toxins

A. fumigatus secretes a number of toxins such as aflatoxin and gliotoxin. Aflatoxin does not have any bearing on virulence of *A. fumigatus*, it is hepatotoxic and carcinogenic. Gliotoxin is immunosuppressive and inhibits phagocytosis by macrophages and T-cell activation (2). It also slows ciliary movement thus making it difficult for the fungal cells to be swept away, and causes damage to the epithelium (33). Most other fungi produce a number of secondary metabolites that have numerous cellular actions, some of which are probably important in pathogenesis.

The role of Calcineurin and Mannitol

Calcineurin acts as a sensor for pathogenic fungi. It is said to influence the expression of several virulence factors. Calcineurin CNAA gene is important for the growth of *A. fumigatus*, and contributes to tissue

invasion (34). Mannitol is especially used by *C. neoformans* in CNS infections where it protects the fungi by preventing oxidative damage. It is produced in large quantities and may contribute to brain oedema (35).

4. CONCLUSION

Fungal diseases as described are important causes of morbidity and mortality worldwide, affecting mostly the immunosuppressed and the immunocompetent as well. The incidences and associated mortalities of invasive fungal diseases have increased as a result of advancement in treatments, and cancers. The ability of some fungal species to cause disease is due to various virulence factors which help with fungal survival and persistence in the host resulting in tissue damage and disease. A knowledge of these virulence factors is important as research continues towards the development of drugs and vaccines effective in the prevention and treatment of fungal diseases.

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