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Severe *Candida* spp. infections: new insights into natural immunity

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Abstract

Invasive infections caused by *Candida* spp. are associated with high mortality. Colonization by *Candida* spp. and the capacity of the host to recognize them as potential pathogens are essential steps in the development of these infections. The major pathogen-associated molecular patterns of *Candida* are mannoproteins, glucans and chitins, which are recognized by C-type lectin pattern recognition receptors such as the mannose receptor, dectin-1 and dectin-2. By the secretion of proteases and toxins, and the formation of hyphae and biofilms, *Candida* spp. are able to enhance their virulence and pathogenicity. Studies in patients with relatively rare immunodeficiencies, such as dectin-1 deficiency, CARD9 deficiency, chronic mucocutaneous candidiasis, hyper-IgE/Job's syndrome and chronic granulomatous disease, have shown the role of dectin-1 and its signalling pathway, which involves interleukins 17 and 22, defensins and phagocytic cells, in defence against *Candida*. These studies also provide insights into how acquired risk factors for fungal infection operate, and may lead to new approaches for immunotherapy.

Keywords:

Candida

Invasive fungal infection

Pathogen-associated molecular patterns

Interleukins

1. Introduction

Invasive infections caused by *Candida* spp. are a major healthcare problem in modern medicine [1]. These yeasts rank as the fourth most common bloodstream pathogen in hospitals in the Western world [2,3] but are associated with the highest mortality among bloodstream infections.

In healthy subjects *Candida* spp., especially *C. albicans*, are present as a commensal. Colonization by *Candida* spp. is almost always the first step in the development of invasive candidiasis. Many exogenous and endogenous factors may lead to impaired host defence against *Candida* spp. and, as a consequence, *Candida* may disseminate into the bloodstream and infect multiple organs [1]. In this paper we take a stepwise approach to reviewing the pathogenesis of severe *Candida* infections and incorporate insights from recent research.

2. *Candida* spp. colonization of mucosal surfaces

At least 30% of healthy individuals are colonized with *C. albicans* at any given moment [1]. The body sites that *Candida* preferably colonize are the oropharynx, vagina and skin, especially skin folds (axilla, groin, perineum). *Candida* produce proteolytic enzymes (such as aspartyl proteinases and phospholipases) and toxins (such as mycotoxin) that affect host defences and enhance their chances of colonizing and invading the host [4–6]. In addition, *Candida* have the ability to switch phenotype to a more virulent form that spontaneously produces mycelia [7], but it is unclear to what extent this occurs at various sites in vivo [8]. The numbers of *Candida* organisms at different body sites is under the control of other locally colonizing flora, especially bacteria. The exact mechanisms by which bacteria control colonization by yeast are only partially understood. Competition for nutrients is considered a major explanation. In the vagina, lactobacilli not only compete for nutrients but also produce hydrogen peroxide, bacteriocins and lactic acid, which create an environment that is hostile to *Candida* spp. [8]. When the colonizing bacterial flora is destroyed by treatment with antibiotics, especially broad-spectrum drugs, yeast colonization will increase.

In diabetic patients, the high glucose content of the tissues is thought to enhance yeast colonization. Oestrogens lead to increased vaginal yeast colonization by enhancing the glycogen content of the vaginal epithelial cells, thereby providing a nutritional source for *Candida* [9]. In addition, *Candida* spp. possess a cytosolic receptor-like structure that induces mycelial formation after exposure to oestrogen [10]. These mechanisms may be responsible for the increased vaginal *Candida* colonization and frequency of symptomatic candidiasis in pregnancy and after the use of contraceptives with high-dose oestrogen [8].

3. Colonization and infection

An important question is how the host is able to discern between harmless *Candida* cells colonizing the epithelium and *Candida* cells that are pathogenic. Here, Janeway's concept of pattern recognition receptors interacting with the surface molecules of pathogens called pathogen-associated molecular patterns (PAMPs) is of key relevance [11]. Several families of pattern recognition receptor have been described: the Toll-like receptors, the C-type lectin receptors, the nucleotide-binding domain leucine-rich repeat-containing receptors, and the retinoic acid-inducible gene I receptors [12].

Much has been learned in recent years about the components of the cell wall of *C. albicans*. Mannans, mannoproteins, β -glucans and chitin, considered to be PAMPs [13], are essential for the structure of *Candida*. Chitin and β -glucans provide the necessary rigidity of the internal skeleton, while a heavily mannosylated layer of mannoproteins covers this layer and forms the surface (Fig. 1.). The mannoproteins, which are utilized by *Candida* to adhere to the epithelial surface, are recognized by the mannose receptor and dectin-2, β -glucans by dectin-1, and chitin by an as yet unidentified receptor.

Most of the research into pattern recognition receptors has focused on their presence on white blood cells, and hence the importance of PAMPs on the epithelial cells of the skin and the mucous membranes of the pharynx, gastrointestinal tract, airways and urogenital tract is not fully appreciated.

These insights have enabled us recently to recognize a mild, rather selective immunodeficiency, dectin-1 deficiency [14]. In a family with three female siblings with chronic onychomycosis and recurrent vulvovaginal candidiasis, we demonstrated that their white blood cells did not produce cytokines when exposed to β -glucans. An abnormality of the cellular receptor dectin-1 was therefore suspected. Sequencing of their dectin-1 gene yielded a tyrosine at position 238, leading to a stop codon. As a consequence a cysteine bond is lost, the three-dimensional conformation of the dectin-1 extracellular domain is lost and the molecule is not expressed at the cell membrane. Heterozygotes with this mutation are not extremely rare and population studies have shown that it has to be considered an old mutation [14]. A propensity for more heavy colonization with *Candida* spp. was demonstrated in heterozygous patients within a cohort of allogeneic bone marrow transplant recipients [15]. A similar clinical picture to homozygous dectin-1 deficiency is seen in the homozygous CARD9 mutation that has recently been described [16]. This is not unexpected, as CARD9 is a signalling molecule downstream of dectin-1.

4. T_H17 lymphocytes and defensins

In the subepithelial tissues, T lymphocytes play a sentinel role in the defence against fungi. Research in our laboratory has demonstrated that *C. albicans* is the most potent known inducer of the differentiation of T helper lymphocytes (T_H) into the T_H17 phenotype [17]. The *Candida* mannan and β -glucan PAMPs are responsible for the induction of the T_H17 response [17]. There is evidence that complement activation, especially factor C5a, contributes to the induction of T_H17 [18]. The T_H17 lymphocytes (and also CD4-/CD8- T cells expressing T-cell receptor $\gamma\delta$) produce and secrete the proinflammatory cytokines interleukin (IL)-17 and IL-22, and these cytokines in turn induce the production of β -defensins by epithelial cells (Fig. 2.) [19,20]. β -defensins are cationic, amphiphilic, antimicrobial peptides of 12–50 amino acids; as they have antifungal activity they are able to limit the outgrowth of colonizing *Candida* [21]. The patients with dectin-1 deficiency described above also have decreased IL-17 production [14].

When there is a lack of control by CD4+ lymphocytes, as occurs in HIV infection, idiopathic CD4 lymphocytopenia or after treatment with the anti-CD52 monoclonal antibody alemtuzumab, an increased outgrowth of *Candida* spp. may occur, leading to infection [22]. Patients with rare immunodeficiency disorders, such as hyper-IgE/Job's syndrome (HIES) and chronic mucocutaneous candidiasis, suffer from mucocutaneous candidiasis (Fig. 2. and Fig. 3.) because of a lack of production of IL-17, IL-22 and β -defensins [23–25]. Because IL-17 also induces chemokines (e.g. IL-8) and the growth factor granulocyte colony-stimulating factor (G-CSF), it induces the differentiation and migration of neutrophils (Fig. 4.) and thereby contributes to natural immunity when *Candida* has gained access to subepithelial tissues [26]. Such invasion may occur when there is physical or chemical damage to the epithelium.

Deficiency of IL-17 and IL-22, as occurs in the clinical disorders mentioned above, may thus predispose to more deep-seated *Candida* infection.

5. Yeasts, hyphae and invasiveness

When colonizing the epithelial surface, *Candida* spp. tend to be present only as yeasts, but when invading the tissues the yeast cells germinate and form hyphae. Hyphae are necessary for tissue invasion, as has been shown experimentally using *Candida* mutants that are unable to germinate at 37°C [27]. Whether the host responds in a different way to yeasts and hyphae is not known.

During invasion of the tissues *Candida* encounter resident macrophages and this leads to the induction of mRNA for cytokines such as IL-1 β and IL-18. These are produced as inactive precursors and for processing into active cytokines the inflammasome, a cytoplasmic protein platform [28], has to be activated in order to produce active caspase 1 (formerly called IL-1 converting enzyme). Whether *Candida* alone are able to activate the inflammasome, and if so by which components, is currently unknown. Neutrophils and monocytes (exudate macrophages) recruited to the site of infection will phagocytose and kill *Candida*, and in addition contribute to cytokine production (Fig. 5.). By contrast with macrophages, monocytes dispose of bioactive caspase-1 and thereby readily process and secrete IL-1 β [29]. The most serious invasive *Candida* infections tend to develop in patients with abnormal neutrophil recruitment, neutrophil dysfunction and, not least, in patients with severe neutropenia [30]. As mentioned above, a deficiency of IL-17, as occurs in HIES, will lead to insufficient neutrophil recruitment from the bloodstream. The cold abscesses that are a hallmark of HIES, and led to its original description as Job's syndrome [31], are a consequence of the poor influx of neutrophils. The most common acquired cause of defective neutrophil recruitment is treatment with glucocorticosteroids and other immunosuppressive drugs. The mechanisms by which glucocorticosteroids affect host defences are multiple [32]. A major mechanism is interference with the expression of adherence molecules on white blood cells [33]. In addition, corticosteroids inhibit the production of IL-17 [34]. A detailed discussion of the mechanisms by which other immunosuppressants affect host defence is beyond the scope of this paper.

The best-studied example of neutrophil dysfunction is, without doubt, chronic granulomatous disease, the group of hereditary phagocyte disorders in which there is defective generation of reactive oxygen intermediates (such as superoxide) due to a mutated NADPH cytochrome oxidase (or one of the proteins of the oxidase complex) in the membrane of the phagocytic cells [35]. Both neutrophils and monocyte/macrophages are defective in chronic granulomatous disease. Although *Aspergillus* spp. infections are the greatest threat to these patients, severe invasive *Candida* infections are quite common [36].

With regard to neutropenia, patients with neutropenia induced by chemotherapy or X-irradiation are at greater risk than those with one of the congenital neutropenia syndromes. The mucosal damage inflicted by chemotherapy or X-rays helps *Candida* to invade the tissues. An additional risk factor is broad-spectrum antibiotics [3], as they enhance the numbers of *Candida* by interfering with bacterial colonization at body surfaces. In addition, indwelling medical devices such as intravenous catheters increase the risk for invasive candidiasis by a number of mechanisms. First, catheters breach in the skin and underlying tissues, providing an easy portal of entry for microorganisms. Second, the foreign material of the catheter forms a barrier to the defence mechanisms of the host and to antimicrobial therapy. This barrier may be enhanced by the formation of biofilms by the infecting microorganism [37]. *C. albicans* makes rather complex metabolically active biofilms consisting of a basal blastospore layer with an overlying matrix of polysaccharides and hyphae [38]. Third, the nature of the infusion fluid, especially when it is parenteral nutrition fluid or highly concentrated sugar solution, contributes to the risk of *Candida* infection by promoting the growth of the fungus [39].

Among patients with normal neutrophil numbers and function the most important risk factors for invasive candidiasis are also systemic antibiotic therapy, the presence of indwelling medical devices (especially a central venous catheter) and total parenteral nutrition [3]. Major abdominal surgery, pancreatitis and renal insufficiency are additional risk factors [3,40,41]. Via the bloodstream, *Candida* spp. tend to lodge in various organs, the most serious localizations being the central nervous system and the endocardium [42,43]. As mentioned above, the host's army in these tissues consists of monocytes/exudate macrophages, tissue

macrophages and neutrophils; T_h cells and natural killer cells also play a role in the combat. In the interplay between these cells a series of cytokines, the most important being IL-1, tumour necrosis factor, IL-18 and interferon (IFN) γ , are essential to activate the candidacidal mechanisms (Fig. 4.). Because of the comorbidity and additional risk factors in these patients, these effector mechanisms often function suboptimally and this leads to the poor prognosis.

6. Immunotherapy for candidiasis

Despite the advent of potent new antifungal drugs, the prognosis of severe candidiasis, especially candidaemia, has not substantially improved in recent years [44]. Part of the explanation is that patients with invasive candidiasis often have severe and potentially fatal comorbidities and hence even very potent antifungal drugs may fail. If we consider the attributable mortality, which is in the order of 40% [41], the conclusion must be that there is room for improvement. Given the knowledge of host defence mechanisms presented in this paper it would be logical to follow the famous quote of Sir Ralph Bloomfield Bonington in George Bernard Shaw's play *The Doctor's Dilemma*: 'Stimulate the phagocytes!' This kind of approach, using either G-CSF, IL-1, IL-18 or IFN γ , has been undertaken in experimental animals and met with improved survival [45–49]; in humans, however, clinical trials are scarce. In a randomized trial in non-neutropenic patients with candidaemia, Kullberg et al. [50,51] found that G-CSF significantly decreased the time to resolution of candidiasis, and patients treated with G-CSF who achieved an increased neutrophil count had improved survival.

As far as we know this study has never been repeated and G-CSF has not yet found its way into the treatment of invasive candidiasis. A randomized controlled clinical trial exploring the effects of recombinant IFN γ is planned to start towards the end of 2010. In addition, it is time to explore other treatments based on the insights that have been acquired in the pathogenesis of severe *Candida* infections.

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[Figure legends]

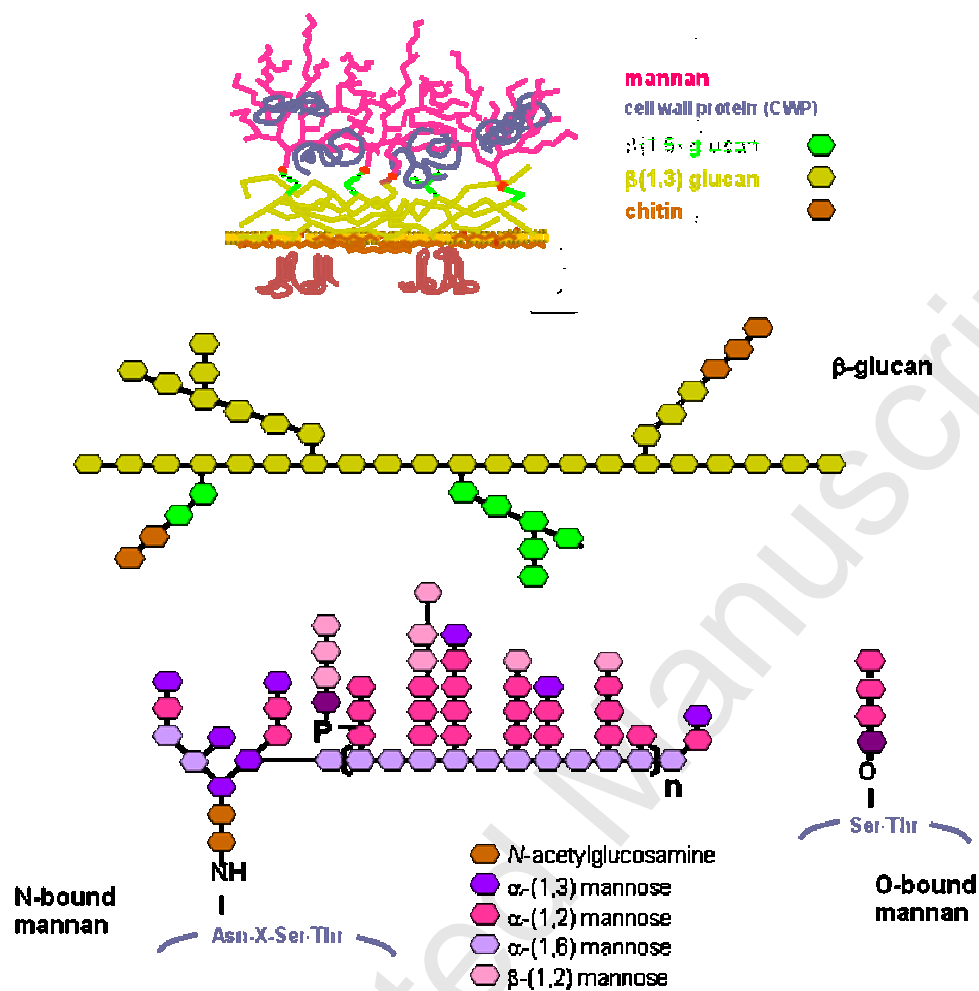
Fig. 1. The major pathogen-associated molecular patterns (PAMPs) of the *Candida albicans* cell wall. The inner layers of the cell wall consist of a rigid skeleton of β -glucans and chitin, while at the surface, heavily mannosylated proteins (with both N- and O-bound mannans) cover and shield the other PAMPs of the cell wall.

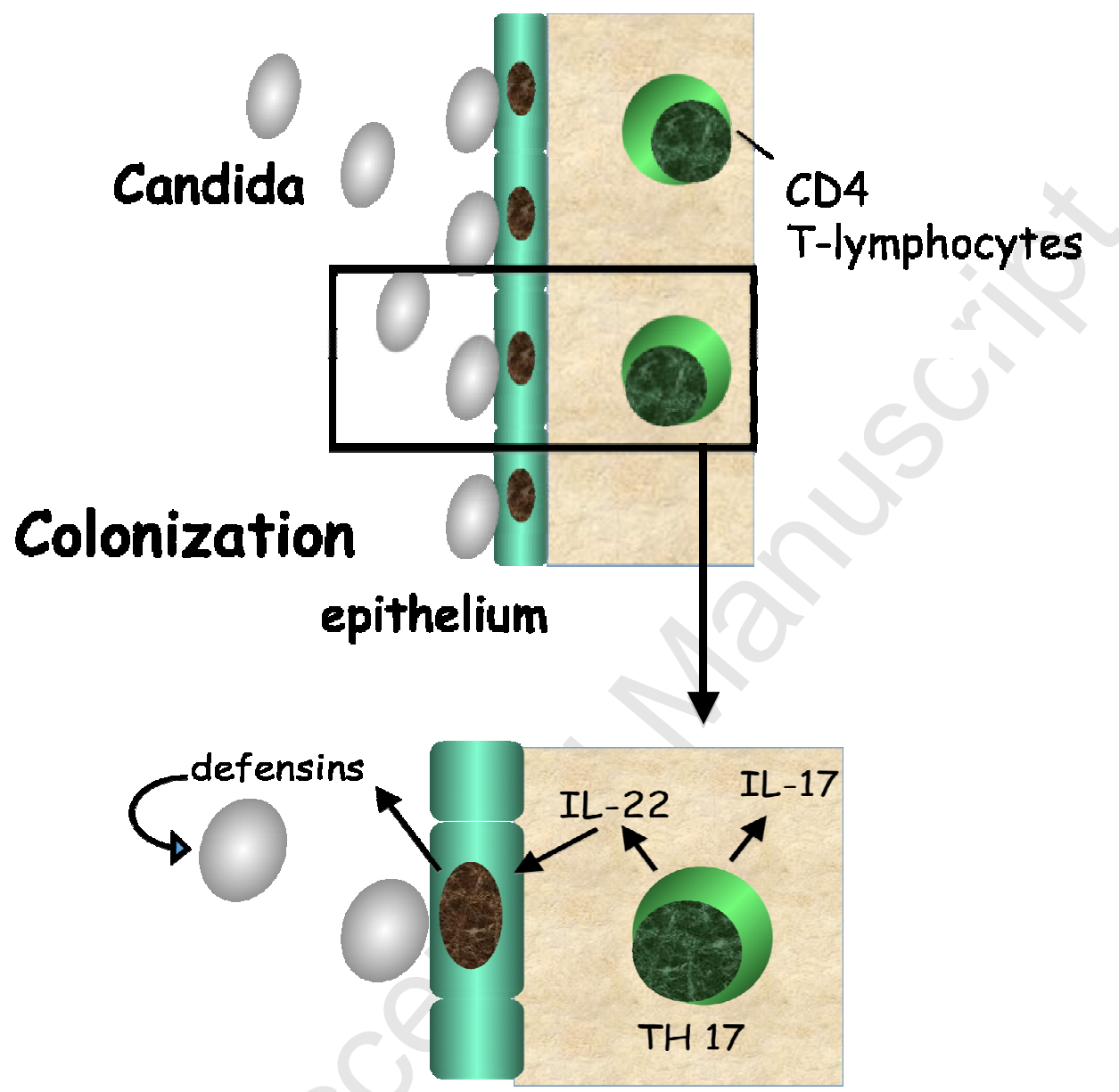
Fig. 2. *Candida* cells colonizing the epithelium are under the control of CD4 lymphocytes that have differentiated into T helper 17 lymphocytes (TH 17). These produce interleukin-17 (IL-17) and interleukin-22 (IL-22). IL-22 stimulates the epithelium to produce β -defensins, which are able to limit the outgrowth of the fungal cells.

Fig. 3. Extensive candidiasis of the feet of a 37-year-old man with chronic mucocutaneous candidiasis.

Fig. 4. When the epithelium is damaged by physical or chemical means the yeast is able to enter the submucosal tissue and start to form hyphae (the branched structures). The entry through the damaged epithelium will release chemotactic substances that evoke recruitment of polymorphonuclear leukocytes (PMN, i.e. neutrophils), which are able to phagocytose the yeasts and hyphae.

Fig. 5. *Candida* in its yeast form as well as its hyphal form encounters the various cells of the host defence. Resident macrophages ($M\phi$) in the infected tissue produce a series of cytokines (interleukin (IL)-12, IL-18, and tumour necrosis factor (TNF) α) to activate CD4 lymphocytes and natural killer (NK) cells to produce and secrete interferon- γ (IFN γ) to enhance the fungicidal capacity of polymorphonuclear leukocytes (PMN) and monocytes (which become exudate macrophages). The resident macrophages also produce IL-1 β , IL-6 and IL-23, which in turn induce T helper 17 lymphocytes (TH17) to produce IL-17. The latter cytokine plays an important role in the attraction of neutrophils.







Accepted

