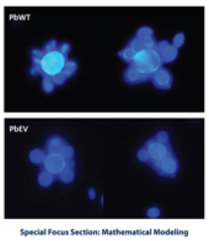
Virulence



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Adhesins in *Candida parapsilosis*: Understudied players in virulence

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Candida species are the leading cause of fungal bloodstream infections that are associated with a very high mortality, especially in immunocompromised patients.[1] The first step of *Candida* infection involves a tight adherence to human cells in the skin, epithelium or endothelium.[2] The ability to stick these host tissues and/or abiotic surfaces such as catheters or prosthetic devices is enabled by genes coding for different families of fungal cell wall adhesins. One of the most extensively studied group of proteins involved in this process belong to the Als (agglutinin-like sequence) family (reviewed in[3]). Despite their broadly acknowledged importance as virulence factors in *C. albicans*, we lack detailed information concerning the biological role of the Als proteins in other *Candida* species such as *C. parapsilosis*.

Over the past 2 decades, *C. parapsilosis* has become an increasingly important human pathogen as it is now the second most commonly isolated *Candida* species from blood cultures worldwide, and even outranks *C. albicans* in some hospitals.[4-7] *C. parapsilosis* typically is a commensal of human skin and is considered to be of low pathogenicity in the setting of intact integument. The species is notorious for its capacity to form biofilms on catheters and other implanted devices, for nosocomial spread by hand carriage, and for persistence in the hospital environment.[7-9] *C. parapsilosis* is of special concern in critically ill neonates, causing more than one quarter of all invasive fungal infections in low birth weight infants in the UK [10] and North America,[11,12] and it is a leading cause of neonatal mortality.

In this issue Bertini and colleagues demonstrate the role of a yet uncharacterized *C. parapsilosis* gene in adhesion to host surfaces and its contribution to the virulence of this species.[13] The authors identified and disrupted a hypothetical, adhesion effecting gene "CPAR2_404800," (ortholog of *C. albicans* ALS genes), using a previously described gene deletion method.[14] After testing the heterozygous and null mutants, the results suggested that CPAR2_404800 does not influence the growth, morphologic potential, or cell wall stressor resisting abilities of *C. parapsilosis*; however, it does play a role in cell adhesion and pathogenicity. Significantly, reduced cell adhesion was observed on human buccal epithelial cells, and a remarkable reduction in virulence was detected *in vivo* using a murine urinary candidiasis model. Hence, the authors provide the first evidence for a direct role of *C. parapsilosis* adhesins in pathogenesis and virulence.

The work by Bertini *et* al[13] highlights the need for more detailed investigations of one of the most important features of the pathogenesis program by fungi—the adhesion to host tissues and cells—not only in *C. albicans* but in other emerging *Candida* pathogens. There are several reports about the different adhesion capacities for individual *Candida* species, including *C. parapsilosis*.[15,16] In general *C. albicans* has a greater capacity to adhere to host tissues, such as epithelial cells and vascular epithelium.[16,17] This difference could be explained due to the presence of more α-L-fucose residues in the *C. albicans* cell wall relative to other speices.[18] Interestingly, despite the fact that *C. parapsilosis* is known to be more a more frequent cause of disease in low birth weight newborns, Falgier et al found that *C. parapsilosis* showed little capacity to adhere to primary immature human enterocytes compared with *C. albicans*.[19] Bertini and coworkers previously showed that *C. parapsilosis* and *C. orthopsilosis* have similar adhesion capacities to human buccal epithelial cells, in contrast the third member of the *C. parapsilosis sensu lato* species complex, *C. metapsilosis*, which displayed a significantly lower adhesive affinity.[15] One of the important roles of fungal adhesins is to bind extracellular matrix (ECM) proteins such as fibronectin, vitronectin and laminin, and a recent study identified Als-like proteins on the surface of *C. parapsilosis* pseudohyphae that can bind to ECM components and thus can serve as the first step to cross mechanical barriers.[20]

On the genomic level, comparative genomic analyses identified an enrichment of these gene families in pathogenic *Candida* species and the absence of ALS orthologs in the *Saccharomyces* calde.[21] In addition, previous work described surprisingly large intraspecies variability in the number of ALS gene family members between *C. parapsilosis* isolates.[22] In *C. albicans*, the family includes 8 genes (ALS1-7 and ALS9;[23]) encoding large cell surface glycoproteins.[3,24] Although the structure of the Als proteins is similar (especially in the N terminal domains) the biological role of the individual ALS members in *C. albicans* appear to differ from each other.[24] Different studies on Als1p and Als3p in *C. albicans* have shown their significant involvement in pathogenesis and virulence,[23] including in

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invasion.[25] Recently an analysis of the presence and distribution of ALS genes in clinical and environmental isolates of *C. parapsilosis* has been performed revealing that different strains code a variable number of ALS genes, ranging from a single member (GA1, CBS1954), to 3 (CBS6318) and 5 (CDC317) members.[22] Phylogenetic analysis reveals a rather complex and highly dynamic genetic process—including gene conversation—shaping the ALS gene family within pathogenic *Candida* species.[22] It is still unclear how this high variability in ALS gene family of *C. parapsilosis* affects host-pathogen interactions.

While growing evidence in various disease models, including mouse and reconstituted human tissues, has demonstrated that *C. albicans* adhesins are key virulence factors as they play an essential role in pathogenesis,[26-28] we have very little information about the role of adhesion in *C. parapsilosis* virulence and pathogenesis. Only a few studies have investigated the virulence properties of *C. paparsilosis* with different adhesion capacity in *in vitro* and *in vivo* systems. The same group that presented the work detailed in this review has previously shown in an experimental vaginitis model in estrogen-treated mice that there are slight differences in disease as demonstrated by fungal burdens between *C. parapsilosis* and *C. metapsilosis*, which correlates with the latter's lower adhesion capacity.[15] This finding is supported by results in a study using a *Galleria mellonella* larvae infection model that found a significantly reduced mortality rate in the larvae infected with *C. metapsilosis* isolates compared to larvae infected with *C. parapsilosis sensu stricto* or *C. orthopsilosis* strains.[29] In contrast, a disseminated candidiasis model showed no significant differences among the *C. parapsilosis sensu lato* species.[30]

Taken together, there is still a substantial gap in our knowledge regarding the detailed genetic determinants of adhesion properties of *C. parapsilosis*, and how these affect the interaction with the human host, including the tendency to disproportionally affect specific groups of patients. In sum, it is incontrovertible that we need a clearer understanding of the role of *C. parapsilosis* cell wall adhesins in the establishment of candidiasis in order to better understand host-pathogen dynamics as well as to develop new strategies to combat this emerging fungal pathogen.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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