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Fungal Infection of Candida Albicans: Genetics, Dimorphism and Pathogenicity

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Abstract – Candida albicans a dimorphic fungus that causes severe opportunistic infections in humans. Recent advances in molecular biology techniques applied to this organism (transformation systems, gene disruption strategies, new reporter systems, relatable promoters) allow a better knowledge of both the molecular basis of dimorphism and the role of specific genes in Candida morphogenesis. These same molecular approaches together with the development of appropriate experimental animal models to analyze the virulence of particular mutants, may help to understand the molecular basis of Candida virulence.

Key words: Candida albicans· Dimorphism· Morphogenesis · Yeast pathogenicity

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INTRODUCTION

Candida albicans is a diploid fungus that grows both as yeast and filamentous cells and a causal agent of opportunistic oral andgenital infections in humans,[3][4] and candidal onychomycosis, an infection of the nail plate. Systemic fungal infections (fungemias) including those by *C. Albicans* have emerged as important causes of morbidity and mortality in immunocompromised patients (e.g.,AIDS, cancer chemotherapy, organ or bone marrow transplantation). *C. Albicans* biofilms may form on the surface of implantable medical devices. In addition, hospital-acquired infections by *C. albicans* have become a cause of major health concerns.

C. albicans is commensal and a constituent of the normal gut flora comprising microorganisms that live in the human mouth andgastrointestinal tract. *C. albicans* lives in 80% of the human population without causing harmful effects, although overgrowth of the fungus results in candidiasis (candidosis). Candidiasis is often observed in immunocompromised individuals such as HIV-infected patients. A common form of candidiasis restricted to the mucosal membranes in mouth or vagina is thrush, which is usually easily cured in people who are not immunocompromised. For example, higher prevalence of colonization of *C. albicans* was reported in young individuals with tongue piercing, in comparison to unpierced matched individuals. To infect host tissue, the usual unicellular yeast-like form of *C. albicans* reacts to environmental cues and switches into an invasive, multicellular filamentous form, a phenomenon called dimorphism.

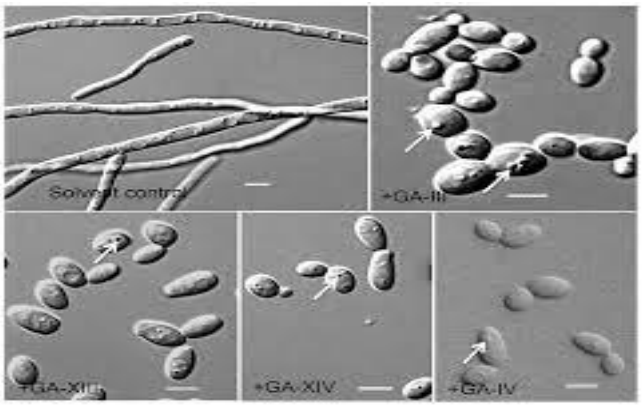


Figure: C.albicans yeast structure

DIMORPHISM

Although often referred to as "dimorphic", C. albicans is in fact polyphenic. When cultured in standard yeast laboratory medium, *C. albicans* grows as ovoid "yeast" cells. However, mild environmental changes in temperature and pH can result in a morphological shift to pseudohyphal growth. Pseudohyphae share many similarities with yeast cells, but their role during candidiasis remains unknown. When *C. albicans* cells are grown in a medium that mimics the physiological environment of a human host, they grow as "true" hyphae. Its ability to form hyphae has been proposed as a virulence factor, as these structures are often observed invading tissue, and strains that are unable to form hyphae are defective in causing infection.

In a process that superficially resembles dimorphism, *C. Albicans* undergoes a process called phenotypic switching, in which different cellular morphologies are generated spontaneously. Of the classically studied strains, one

that undergoes phenotypic switching is WO-1, which consists of two phases: one that grows as round cells in smooth, white colonies and one that is rod-like and grows as flat, gray colonies. The other strain known to undergo switching is 3153A; this strain produces at least seven different colony morphologies. In both the WO-1 and 3153A strains, the different phases convert spontaneously to the other(s) at a low frequency. The switching is reversible, and colony type can be inherited from one generation to another. While several genes that are expressed differently in different colony morphologies have been identified, some recent efforts focus on what might control these changes. Further, whether a potential molecular link between dimorphism and phenotypic switching occurs is a tantalizing question.

In the 3153A strain, a gene called *SIR2* (for silent information regulator), which seems to be important for phenotypic switching, has been found. *SIR2* was originally found in *Saccharomyces cerevisiae* (brewer's yeast), where it is involved in chromosomal silencing—a form oftranscriptional regulation, in which regions of the genome are reversibly inactivated by changes in chromatin structure (chromatin is the complex of DNA and proteins that make chromosomes). In yeast, genes involved in the control of mating type are found in these silent regions, and *SIR2* represses their expression by maintaining a silent-competent chromatin structure in this region. The discovery of a *C. albicans SIR2* implicated in phenotypic switching suggests it, too, has silent regions controlled by *SIR2*, in which the phenotype-specific genes may reside.

Another potential regulatory molecule is *Efg1p*, a transcription factor found in the WO-1 strain that regulates dimorphism, and more recently has been suggested to help regulate phenotypic switching. *Efg1p* is expressed only in the white and not in the gray cell-type, and overexpression of *Efg1p* in the gray form causes a rapid conversion to the white form.

So far, very few data suggest dimorphism and phenotypic switching use common molecular components. However, it is not inconceivable that phenotypic switching may occur in response to some change in the environment, as well as being a spontaneous event. How *SIR2* itself is regulated in *S. cerevisiae* may yet provide clues as to the switching mechanisms of *C. albicans*.

MORPHOGENESIS

C. albicans can grow as either yeast (round or oval cells) or filamentous cells, the latter comprised of pseudohyphae (chains of ellipsoidal cells with constricted septa between mother and daughter cells) and hyphae (long filaments with no constriction at septa) . Both yeast and filamentous cells have been identified in infections and there is strong evidence that the yeast-to-filamentous growth transition is essential for virulence.. C. albicans mutants that have defects in the yeast-to-filamentous growth transition have markedly reduced ability to become internalized and cause endothelial cell injury in vitro. Also, C. albicans mutants defective in the yeast-to-filamentous growth transition are avirulent in a mouse model of disseminated Candidiais .

Small Molecule Reagents in Understanding Biological Mechanisms

The use of small organic molecules in deciphering complex biological processes has been tremendously fruitful. For example, much of what is known about actin-based processes comes from studies using specific inhibitors of actin structure or function such as the cytochalasins and latrunculins. In addition, molecules such as nocodazole have been used extensively as synchronization tools in the study of the cell division cycle in eukaryotes. These types of small molecules have proven invaluable because they interact with their target proteins as agonists or antagonists in a highly specific manner, which allows definitive conclusions or strong inference to be drawn regarding a protein's function in a particular process. This type of approach is analogous to a "reverse genetic" approach in that molecules are used to study known protein targets that are tested for their involvement in cellular processes.

Since C. albicans is an obligate diploid with no known sexual cycle, classical genetic screens to dissect pathogenically related processes are not possible in this organism. Chemical genetics (i.e., the use of bioactive small molecules to inhibit specific cellular functions) has the potential to circumvent this inherent difficulty and greatly advance research on this important human pathogen.

PATHOGENICITY

The pathogenicity of C. albicans makes important understanding its relationship with the host. Experimental animal models Animal models have been developed to study, from the point of view of the parasite, virulence determinants and, from the point of view of the host, the contribution of the different aspects of the immune response to control the infection; as well as to study the in vivo fungistatic or fungicidal capacity of different drugs. In these models, different types of infection are induced, as will be detailed below, and the ability of Candida to elicit lesions in different tissues, or even the death of the animals is analyzed. Of the existing models, the most used is the murine one since mice are cheaper than rats, guinea-pigs and rabbits, and because of the similarity of the murine systemic infection to that found in humans.

Types of assays

(i) Cutaneous infections. Generally, an area of the animal's skin is slightly scarred and the yeast is inoculated. The development of the skin colonization

is monitored and samples are taken at different times. For more details, see the review by Ray.

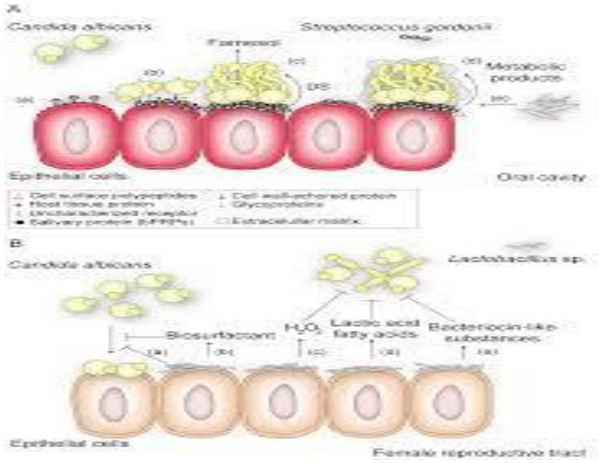
(ii) Vaginitis. This is usually induced in ovariectomized and treated with oestrogen rats and mice. Previously, untreated hamsters have also been used.

(iii) Intestinal infection. These infections are difficult to induce in adult mice but not in six-day-old ones , or in germ-free mice, which are able to retain the infection for several weeks, thereby enabling its study.

(iv) Systemic infection. Systemic infection with C. albicans is induced in mice, rats, guinea-pigs and rabbits. Like the above models, these are sometimes used to assess the efficiency of antifungal agents although, more recently, they have also been used to study virulence determinants.

Two types of systemic infections can be set up: lethal, in which the survival time is measured, and non-lethal, in which the severity of the infection is measured by fungal cell counts (CFUs) in internal organs or by the lesions produced by the microorganism in them (observed by anatomical pathology studies).

(v) Other infections: - The rat palate candidiasis model is used to study a kind of lesion frequently occurring in individuals with dentures . - Models of pielonephritis have been developed in rabbits, as well as models of endocarditis and endophthalmitis . - A murine model has been developed for the study of muguet: air is injected into the backs of mice and C. albicans is inoculated into the subcutaneous sac thus formed.



Antifungal agents

Use of local antibiotic agents in root canal infection has been of interest for decades. However, there is no evidence that antibiotic cocktails would completely disinfect dentine or give higher clinical success rates. Neither is there evidence that local antimitotic substances would give better results than 'traditional' local disinfecting agents. Topical antibiotic agents always cause a local concentration gradient. Microorganism residing in dentinal tubules or per apical lesions exposed to sub lethal concentration may therefore develop resistance. Therefore, fungal antibiotics should be considered locally and systemically only for the treatment of acute apical periodontitis with severe symptoms after microbiological diagnosis.

CONCLUSION

C. albicans is by far the most common yeast in endodontic infections. Yeasts can be found in low numbers both from primary infections as well as from post-treatment infections. The number of yeast cells in the root canal is usually much lower than that of bacteria, and it is uncertain at present whether yeasts can survive outside the root canal in the periapical area in 'extraradicular infections'. The ability of C. albicans to interact with dentine may be important for its ability to survive in the ecologically demanding environment of the necrotic or treated root canal. Although C. albicans and other yeasts are resistant to some locally used disinfecting agents such as calcium hydroxide in vitro, there is no solid evidence that their eradication from the root canal is a clinical problem. C. albicans is more sensitive to sodium hypochlorite than E. faecalis, and it is also rapidly killed by low concentrations of chlorhexidine. In the future, combinations of present and new disinfecting agents and substances that may act in a synergistic manner with dentine may take us closer to the goal of complete dentine disinfection.

REFERENCES

1. Ashman RB, Fulurija A, Robertson TA, Papadimitriou JM (1995) Rapid destruction of skeletal muscle fibers by micelial growth forms of Candida albicans. Exp Mol Pathol 62:109–117

2. Bailey DA, Feldmann PJF, Bovey M, Gow NAR, Brown AJP (1996) The Candida albicans HYR1 gene, which is activated in response to hyphal development, belongs to a gene family encoding yeast cell wall proteins. J Bacteriol 178:5353–5360

3. Barton RC, Gull K (1992) Isolation, characterization, and genetic analysis of monosomic, aneuploid mutants of Candida albicans. Mol Microbiol 6:171–177

4. Becker JM, Henry LK, Jiang W, Koltin Y (1995) Reduced virulence of Candida

albicansmutants affected in multidrug resistance. Infect Immun 63:4515–4518

5. Birse CE, Irwin MY, Fonzi WA, Sypherd PS (1993) Cloning and characterization of ECE1, a gen expressed in association with cell elongation of the dimorphic pathogen Candida albicans. Infect Immun 61:3648–3655

6. Braun BR, Johnson AD (1997) Control of filament formation in Candida albicans by the transcriptional repressor TUP1. Science 277:105–109

7. Brown DH Jr, Slobodkin IV, Kumamoto CA (1996) Stable transformation and regulated expression of an inducible reporter construct in Candida albicans using restriction enzyme-mediated integration. Mol Gen Genet 251:75–80

8. Bulawa CE, Miller DW, Henry LK, Becker JM (1995) Attenuated virulence of chitin-deficient mutants of Candida albicans. Proc Natl Acad Sci USA 92:10570–10574

9. Calderone RA (1993) Molecular interactions at the interface of Candida albicans and host. Arch Med Res 24:275–279

10. Sudbery, P., N. Gow, and J. Berman, The distinct morphogenetic states of Candida albicans. Trends in Microbiology, 2004. 12: p. 317-324.

11. Saville, S.P., et al., Engineered control of cell morphology in vivo reveals distinct roles for yeast and filamentous forms of Candida albicans during infection. Eukaryotic Cell, 2003. 2: p. 1053- 1060.

12. Gow, N.A., A.J.P. Brown, and F.C. Odds, Fungal morphogenesis and host invasion. Current Opinions in Microbiology, 2002. 5: p. 366-371.

13. Phan, Q.T., P.H. Belanger, and S.G. Filler, Role of hyphal formation in interactions of Candida albicans with endothelial cells. Infection and Immunity, 2000. 68(6): p. 3485-3490.

14. Lo, H.J., et al., Nonfilamentous C. albicans mutants are avirulent. Cell, 1997. 90(5): p. 939-949.

15. Degterev, A., et al., Identification of small-molecule inhibitors of interaction between the BH3 domain and Bcl-xL. Nat Cell Biol, 2001. 3(2): p. 173-82.

16. Ward, G.E., K.L. Carey, and N.J. Westwood, Using small molecules to study big questions in cellular microbiology. Cellular Microbiology, 2002. 4: p. 471-482.

17. Peterson, J.R. and T.J. Mitchison, Small molecules, big impact: a history of chemical inhibitors and the cytoskeleton. Chemistry & Biology, 2002. 9: p. 1275-1285.

18. Nehil, M.T., et al., Uncovering genetic relationships using small molecules that selectively target yeast cell cycle mutants. Chemical Biology and Drug Design, 2007. 69: p. 258-264.

19. Lokey, R.S., Forward chemical genetics: progress and obstacles on the path to a new pharmacopoeia. Current Opinion in Chemical Biology, 2003. 7: p. 91-96.

20. Danial, N.N. and S.J. Korsmeyer, Cell death: Critical control points. Cell, 2004. 116(2): p. 205-219.