**Vocation, location, vocation: Researching Candida pathogenesis**

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*Candida albicans* is the fourth leading cause of nosocomial infections. Its rise to infamy, along with other mycological infections, began in the 1980s with the onset of HIV, improved medical technology including increased use of implants, catheters, antibiotics, and immunosuppressive therapies. The predisposing symptoms of candidiasis are well documented. Many virulence characteristics have been attributed to Candida, yet in the end, a study ultimately demonstrates that while this ‘virulence factor’ may contribute to pathogenesis, it is not exclusively required. The ultimate goal of Candida is to survive, and it has a variety of means to succeed at this. Certainly, more than one strategy is utilized by Candida, and when one is not successful, it can initiate another. The fungus affects pathogenesis via redundant pathways, and thus the specific mechanisms which result in pathogenesis remain elusive.

Due to high morbidity and mortality, it remains significant to search for new therapies for Candida infections. Consequently, how Candida colonization results in pathogenesis is a key question. A common approach is to test Candida mutants that are deleted in a specific gene of interest (GOI). This GOI is normally rationally chosen based on its function or purported function (vocation). The mutant is then run in a gambit of in vitro phenotypic tests and in ‘appropriate’ in vivo models (location). The goal is to confirm a role for this gene in pathogenesis. The role it plays may depend on the site of infection (vocation).

Pathways required for survival would be obvious venues for study. Indeed studies with an isogenic set of mutants with variable phenotypic defects, including filamentation, demonstrated that the trait most correlated with virulence was the ability of the mutant to exit lag phase growth at physiological temperature. In this instance it could be a battle of numbers with the immune system. However, there are inherent difficulties in studying survival pathways. These include essentiality of the pathway and/or individual genes; and overall homology of Candida and mammalian housekeeping processes. Therefore, developing non-toxic disruptive strategies are often problematic.

Consequently, Candida research has focused on putative virulence factors of Candida which includes, though not exclusively, proteases, adhesins, biofilm formation, and pathways involved in filamentation and phenotypic switching. The most rigorously researched virulence attribute is the process of filamentation. Mutants significantly defective in filamentation when tested under vigorous conditions in vitro are normally attenuated in virulence in the majority of in vivo models. On the other hand, mutants that are variably defective in filamentation and differentiation pathways in vitro are often not attenuated in virulence in vivo. This exemplifies the redundancy or perhaps resiliency in Candida. The most convincing studies of the role of filamentation have been performed with inducible mutants where it is demonstrated that the strain is virulent only when induced to filament. However, studies also demonstrate that the yeast form is required since strains locked in the filamentous form are avirulent. The most widely accepted theory is that both forms are required for virulence and this is largely based on inducible transcription factor studies. Interestingly, an older study reported a strain locked in the yeast form was virulent. So is it the morphology or proteins that are normally differentially expressed and/or secreted during these stages that are responsible for pathogenesis? While filamentation is most likely required for optimal (on the Candida side) pathogenesis, there may be more suitable pathways to target for antifungal therapies.

Rational pathways to research in this vein are the protein sorting pathways. This would include the cellular trafficking/sorting pathways. Although well characterized in *Saccharomyces cerevisiae*, only a handful of laboratories are addressing the importance of these processes in Candida. However, their importance in virulence is obvious as they function in protein secretion, growth, differentiation, and recycling of nutrients. The goal would be to identify species-specific functions and/or genes. The most commonly studied genes in this pathway in Candida have been vacuolar and genes involved in autophagy. Proper vacuolar biogenesis is required for filamentation and thus attenuated virulence has been demonstrated for some vacuolar mutants. It may make more sense to target genes that are required for the structural biogenesis of hyphae than the actual process of morphogenesis due to the multiple filamentation induction pathways.

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However, the vacuolar sorting pathways demonstrate redundancy, as well. If one looks to study an ‘early’ gene; one that blocks vacuole formation in its entirety, the gene is either essential or the resulting mutant is ‘sick’ and attenuated in growth. Therefore, it is difficult to dissect how this gene contributes to virulence. So while studies show that the ability to form vacuoles is required for filamentation; it is also required for growth, and thus we are back at square one with regards to how Candida causes pathogenesis.

In this edition, Rane et al, have focused on VPS4, a gene involved in the prevacuolar sorting pathway. This pathway is required for filamentation; it is also required for growth, and virulence. So while studies show that the ability to form vacuoles. Therefore, it is difficult to dissect how this gene contributes to virulence. It is not clear how this pathway is involved in the evolution of host-parasite interactions. No potential conflicts of interest were disclosed.

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