Immune-Deficient <i>Drosophila melanogaster</i>: A Model for the Innate Immune Response to Human Fungal Pathogens

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Immune-Deficient *Drosophila melanogaster*: A Model for the Innate Immune Response to Human Fungal Pathogens

Anne-Marie Alarco, Anne Marcil, Jian Chen, Beat Suter, David Thomas, and Malcolm Whiteway

We explored the host-pathogen interactions of the human opportunistic fungus *Candida albicans* using *Drosophila melanogaster*. We established that a *Drosophila* strain devoid of functional Toll receptor is highly susceptible to the human pathogen *C. albicans*. Using this sensitive strain, we have been able to show that a set of specific *C. albicans* mutants of different virulence in mammalian infection models are also impaired in virulence in *Drosophila* and remarkably display the same rank order of virulence. This immunodeficient insect model also revealed virulence properties undetected in an immunocompetent murine model of infection. The genetic systems available in both host and pathogen will enable the identification of host-specific components and *C. albicans* genes involved in the host-fungal interplay. The Journal of Immunology, 2004, 172: 5622–5628.

*Candida albicans* is an opportunistic human pathogen that asymptptomatically colonizes a wide variety of body locations. However, upon alteration of immune system functions, *C. albicans* can proliferate and cause infections termed candidiasis. The significance of our understanding of these fungal infections has been heightened by the increased incidence of candidiasis, primarily due to the expansion of the immunocompromised population associated mostly with the AIDS pandemic and the wider use of medical therapies altering the immune system such as anticancer treatments and organ transplantation.

Although both innate and acquired immunity play important roles in the resistance of mammals to *C. albicans* infections (1, 2), the innate immune response is the first line of defense against *C. albicans* in the systemic circulation (3, 4). Model organisms have proven to be powerful tools for the elucidation of many biological processes. Mammalian models have been developed to explore the very complex relationship between *C. albicans* and its hosts (5, 6).

Recently, genetically well-defined model organisms such as the fruit fly *Drosophila melanogaster* and the nematode *Caenorhabditis elegans* have been used to decipher diverse host-pathogen interactions (7–11). *Drosophila*, although devoid of an adaptive immune system, harbors an innate immune response with striking similarities with plant and mammalian defense mechanisms (12). The *Drosophila* innate immune response uses pattern recognition receptors, which, depending on the receptor, activate phagocytosis by plasmatocytes (the equivalent of mammalian macrophages (13)), proteolytic clotting cascades in the hemolymph, and production of antimicrobial peptides (AMPs) in the fly fat body (14, 15). Interestingly, infection of *Drosophila* with different pathogens leads to the preferential induction of the appropriate group of AMP (8). Fungal infection results in the induction of an antifungal peptide, drosomycin, but not of the antibacterial peptide diptericin (7, 16). The expression of drosomycin is controlled by a signaling pathway orchestrated by the Toll receptor (7, 16). Identification of Toll-like receptors (TLRs) in mammals revealed that these proteins regulate signaling pathways similar to that of the *Drosophila* Toll-dependent pathway (17, 18).

Our work establishes that *Drosophila* is an appropriate host for *C. albicans* and provides a powerful model to study the interplay between pathogen virulence and the host innate immune system.
Construction of a GFP-CAI4 strain

An ADH1 promoter driving green fluorescent protein (GFP) expression plasmid was constructed from a Renilla luciferase expression plasmid as follows. A 1.5-kb NotI-EcoRV fragment from pYPB1-ADHPl (20) was blunt ended and subcloned in Smal-digested pCRW3 (21). The resulting plasmid, pAM1.3, was digested with NotI-SacI, generating a 2.8-kb fragment containing the ADH1 promoter, luciferase gene, and WH1 terminator sequence. This fragment was subcloned in the Smal-digested pJA39 (a kind gift from J. Ash, Montreal, Canada) to generate pAM3. A 723-bp fragment, containing the GFP gene, was obtained by HindIII-Pol digestion of pYeGFP3 (22), blunt ended, and subcloned in XhoI-BglIII-digested and blunt ended pAM3 to remove the luciferase gene. The resulting plasmid, pAM5.6, also contained the CARS, the TRP locus, and the URA3 selectable marker. It was transformed in CAI4 (URA3) strain using the rapid lithium acetate method (23). Transformants were streaked on -URA plates and replica plated on yeast extract peptone dextrose (YEPD). After two rounds on -URA followed by replica plating to YEPD, clones that stably maintained the selectable marker were identified.

Yeast manipulations

The C. albicans and Saccharomyces cerevisiae strains used in this study are listed in Table I. Yeasts were grown in YEPD medium at 30°C.

Northern blot analysis

Total RNA was extracted from 20 adult flies using TRizol (Invitrogen, Carlsbad, CA) according to the manufacturer’s specification. RNA samples (10 μg) were electrophoresed on a 7.5% formaldehyde-1% agarose gel and transferred by capillarity to a ½-Probe nylon membrane (Bio-Rad Laboratories, Mississauga, Ontario, Canada). Detection of specific RNAs was performed by hybridization with 32P-labeled DNA probes as previously described (24). PCR-generated probes were used for the detection of metchnikowin (forward, 5'-GCCACCGAGCTAAGATG; reverse, 5'-AAACGACATCAGCAGTGTG) and RP49 (forward, 5'-CGTGAA GAAGGCCACCAA; reverse, 5'-GATCTTAAGCTTACTCG). A probe for drosomycin was generated by digesting plasmid pMC804 (19) with EcoRI and HindIII. Densitometry analyses (data not shown) were performed using the public domain NIH Image program (developed at the National Institutes of Health and available on the Internet at http://rsb.info.nih.gov/nih-image).

Results

The human pathogen C. albicans can infect the fruit fly D. melanogaster

Several studies have shown that infection of D. melanogaster with various pathogens can be achieved through pricking of the dorso-lateral cuticle of the fly with a needle dipped in a concentrated pathogen pellet (7, 9). This bypasses the natural defense mechanisms that are found on the cuticle of the adult fly and has been used to study the behavior of nonentomopathogen organisms in Drosophila (9, 25). We used a C. albicans strain carrying an integrated version of the GFP gene (CAI4-GFP), which allowed us to follow the progression of the infection through epifluorescence of anesthetized flies. One hour after Drosophila infection with CAI4-GFP, fluorescence can detected surrounding the site of pricking (Fig. 1A). In some flies, the infection progresses from the initial infection site to neighboring tissues (Fig. 1A; 48 h), leading eventually to multiplication of the fungus in the whole Drosophila body cavity.

C. albicans is a dimorphic fungus. It has been suggested that the yeast-to-hyphae transition plays a pivotal role in virulence, allowing C. albicans to penetrate mammalian host tissues (26). It was thus of interest to examine the morphology of the CAI4-GFP strain, injected as blastospores, in our insect model. Flies infected for 48 h with C. albicans and showing strong fluorescence under microscopy were selected. Whole fly bodies were then crushed and examined microscopically. C. albicans remained primarily with the crushed tissues (presumably muscles), while very few fungal cells were found in the hemolymph (data not shown). C. albicans proliferated extensively as pseudohyphae, with some yeast forms visible (Fig. 1B, top). Thus, in a manner similar to that which occurs in a mammalian host model, proliferation within tissues seems to be linked with C. albicans morphological switching.

We further characterized the infection by determining the survival of flies infected with the virulent C. albicans strain SC5314. Wild-type Drosophila is highly resistant to infection with C. albicans, with an average survival of 85%, 48 h postinfection (Fig. 2). Thus, even though we were able to bypass the physical barrier.

Table 1. C. albicans and S. cerevisiae strains used in this study

<table>
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<tr>
<th>Strains</th>
<th>Relevant Genotype</th>
<th>Reference</th>
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<tbody>
<tr>
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<td>URA3/URA3</td>
<td>56</td>
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<tr>
<td>CAI4-GFP</td>
<td>URA3-GFP</td>
<td>This study</td>
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<td>24</td>
</tr>
<tr>
<td>D665-1A (S. cerevisiae)</td>
<td>URA3/URA3 Mat a</td>
<td>CSH stock</td>
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</tbody>
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FIGURE 1. Infection of D. melanogaster with CAI4-GFP. GFP expressing C. albicans was injected in Drosophila. A, Flies were observed by epifluorescence microscopy 1 and 48 h postinfection. B, Infected flies 48 h postinfection were crushed in Drosophila Ringer’s solution and observed under light microscopy or epifluorescence. *, Yeast-like cell; **, Pseudohyphae cells.
of the cuticle of *Drosophila*, the fly has significant defenses against infection with *C. albicans*. This is consistent with the fact that *Candida* species have not often been reported as entomopathogens (27). Deletion mutants of *C. albicans* affecting the virulence in rodent models have been characterized. Among those, the *cdc35*, which carries a deletion for the gene coding for adenylyl cyclase, and *cla4*, carrying a deletion in a p21-activated kinase homolog, had been shown to be avirulent in mouse models of hematogenously disseminated candidiasis (28, 29), whereas in a similar model, the *sap4–6* strain, deleted of three aspartyl-proteases, was strongly attenuated in virulence (30). In wild-type *Drosophila*, all of these mutants were also avirulent (Fig. 2), thus indicating that the fruit fly is a useful host model for the study of *C. albicans*.

**Infection of D. melanogaster with *C. albicans* induces drosomycin expression**

*Drosophila* possesses pathogen recognition receptors that will induce, upon activation, signaling pathways leading to the production of AMPs (15). Infection of adult *Drosophila* with a fungal entomopathogen or Gram-positive bacteria induces most notably the production of the antifungal peptide drosomycin in the *Drosophila* fat body, the equivalent of the mammalian liver (7, 31). We tested the production of drosomycin in response to *C. albicans* infection with a transgenic *Drosophila* line expressing a GFP-drosomycin fusion protein (19). Injected wild-type *C. albicans* SC5314 gave strong drosomycin-GFP expression after 48 h when compared with control flies pricked with a clean needle (Fig. 3). Similar drosomycin-GFP expression levels were also observed upon challenge of the transgenic flies with the *C. albicans* mutants *sap4–6, cla4*, and *cdc35* (Fig. 3). Thus, *C. albicans* is recognized by *Drosophila* as a pathogen, leading to the activation of signaling pathways causing drosomycin levels to increase.

The production of AMPs by the fat body and their secretion in the hemolymph is a component of the *Drosophila* innate immune response (32). Among these peptides, drosomycin and metchnikowin have been shown to display antifungal activity (31, 33) and are transcriptionally up-regulated upon fungal challenge (7, 34). We monitored drosomycin and metchnikowin transcript levels upon challenge with *C. albicans* using Northern blot analysis (Fig. 4). The results confirmed those obtained with the drosomycin-GFP and showed that drosomycin and metchnikowin transcript levels increase over time after infection with wild-type and mutant *C. albicans* of Oregon R (Fig. 4, compare lane 2 with lanes 4, 5, 6, and 7). Conversely, there was no effect on the expression levels of diptericin, which encodes an antibacterial peptide (data not shown; Ref. 7). Drosomycin and metchnikowin transcripts are also elevated after challenge of *Drosophila* with heat-killed *C. albicans* (Fig. 4, lane 8), suggesting that recognition of this pathogen by the flies is similar to mammalian recognition.

**FIGURE 2.** Pathogenicity of *C. albicans* in *D. melanogaster*. Two- to 4-day-old Oregon R females were infected with wild-type *C. albicans* (SC5314) or with *C. albicans* carrying different gene deletions (*cdc35, sap4–6*, and *cla4*). A prototroph diploid *S. cerevisiae* strain was also used. Control flies (CTL) were pricked with a clean needle in the thorax. Survival rates did not change significantly after 48 h. Results are presented as the mean of three independent experiments with SDs.

**FIGURE 3.** Expression of drosomycin-GFP in response to *C. albicans*. Two- to 4-day-old transgenic female *Drosophila* carrying a drosomycin-GFP transgene were infected with various strains of *C. albicans* and observed through epifluorescence 48 h postinfection. HK, heat killed; CTL, flies were pricked with a clean needle.
of fungal heat-resistant α-linked mannans and β-linked glucans (35–37).

Resistance of Drosophila to infection with C. albicans is dependent on the Toll receptor

Infection of Drosophila by the entomopathogenic fungus Beauvaria bassiana leads to an up-regulation of genes encoding AMPs, via the activation to the Toll pathway (7, 8). Furthermore, it was shown that Drosophila Toll mutants, in which Toll expression is abolished, are very sensitive to fungal infection and have concomitantly a markedly reduced Toll-dependent AMPs (7, 8). We examined the role of the Toll pathway in C. albicans infection using Toll transheterozygotes that carried a loss-of-function allele of Toll and a thermosensitive allele of Toll. The susceptibility of the Toll mutant flies to C. albicans was determined as for the wild-type flies. The Toll mutants proved to be highly susceptible to the wild-type C. albicans SC5314, with an average survival rate of ~15% after 48 h (Fig. 5) compared with the OregonR wild-type flies (Fig. 2). This susceptibility is dose dependent (data not shown). Furthermore, the death of Toll mutant flies correlates with massive proliferation of C. albicans throughout the body of the insect with no external signs visible (data not shown).

The susceptibility of the Toll mutants to infection with C. albicans was also assessed by comparing the total fungal load of wild-type and Toll mutant flies following infection with C. albicans (Fig. 6). These data show that C. albicans is able to stably maintain itself in the OregonR flies over 12 h postinfection, with little change in CFU over that time period (Fig. 6). In contrast, CFU obtained for infected Toll mutants increased readily 6 h postinfection, and active proliferation of the pathogen was maintained up to 12 h postinfection (Fig. 6).

The increase in drosomycin and metchnikowin transcript levels observed in wild-type flies following infection with C. albicans is strongly reduced in the Toll mutants (Fig. 4, compare lanes 2, 3, and 4). It is thus tempting to attribute the susceptibility of the Toll mutants to challenge with C. albicans to insufficient levels of drosomycin. Indeed, this hypothesis is supported by the recent demonstration that reinnervation of drosomycin in Drosophila impaired multiple AMP production was sufficient to restore wild-type susceptibility to the fungi Neurospora crassa and Fusarium oxysporum (38).

We examined the susceptibility of the Toll mutants to our panel of C. albicans mutant strains. Infection with the cdc35, cla4, and sap4–6 mutants shows that all these strains display, to different extents, a reduced virulence toward the Toll mutants when compared with SC5314 (Fig. 5). This is evident through both the slower effect on viability and the higher survival rates of the Toll flies infected with our C. albicans mutants. Comparing the survival of Toll mutants 48 h postinfection with the different mutants, >90% of the flies infected survived infection with the cdc35 strain, compared with an average of 60% survival in the infections with the cla4 and sap4–6 mutants (sap4–6 mutants killing faster than cla4 mutants) and 15% with the wild-type C. albicans SC5314 over the same period. These results are in agreement with the body of work that explored the effects of cla4 and sap4–6 deletions on virulence. Indeed, compared with the cdc35 strain, the cla4 and sap4–6 mutants do not display any in vitro growth rate difference under our growth conditions (29, 30). In addition, the increased ability of the sap4–6 and cla4 mutants to kill the Toll mutants compared with cdc35 may also be associated with their ability to undergo pseudohyphal differentiation (29, 39–41). Of all the C. albicans strains used in our study, the cdc35 knockout strain displays the most severely reduced virulence. These results are correlated with the fact that the cdc35 strain is unable to show any

FIGURE 5. Infection of Drosophila Toll mutants with C. albicans. Two-to 4-day-old female Toll transheterozygotes were infected with wild-type C. albicans (SC5314) or with C. albicans carrying different gene deletions (cdc35, sap4–6, and cla4). A prototroph diploid S. cerevisiae strain was also used. Results presented are the means of four independent experiments with SD.

FIGURE 6. Fungal load of infected Drosophila. Wild-type OregonR flies and Toll transheterozygotes were infected with C. albicans SC5314. Groups of 10 flies were collected immediately after infection (0) or at 6, 9, and 12 h postinfection. Collected flies were crushed in Drosophila Ringer’s solution using an Eppendorf and an adapted grinder. Serial dilutions were plated on YEPD agar and incubated for 2 days at 30°C, and CFU were counted. Results are the mean of two experiments.
sign of morphological differentiation under a multitude of conditions and displays a reduced growth rate (28). Interestingly, our model also indicates that the cdc35 mutant is not totally avirulent, because the survival associated with infection with the cdc35 strain decreases significantly 48 h postinfection, reaching ~45% after 96 h (Fig. 5). The inability of S. cerevisiae to have any effect on the survival of the Toll mutants further supports the idea that the cdc35 mutant still contains some virulence potency (Fig. 5). Taken together, our results establish that the ranking of virulence of these C. albicans strains in Toll mutants, i.e., SC5314 > sap4–6 > cla4 > cdc35, is similar to that which is observed in mammals.

We examined the morphology displayed by our panel of C. albicans strains proliferating in infected Toll mutant flies. As was observed for infection in wild-type flies, SC5314 in Toll mutants was a mixture of yeast-like cells together with pseudohyphae attached to the host tissue (Fig. 7). Observation of Toll mutants infected with the sap4–6 and cla4 mutants shows that most of the cells of both strains display germ tubes and are mainly associated with Drosophila tissue, as was seen for infection with the wild-type SC5314 strain (Fig. 7). The differentiated cla4 mutant cells observed inside the fly showed aberrant morphologies characteristic of this strain (29). Proliferating cells of the cdc35 strain in the Toll mutants are, as for SC5314, mainly associated with tissue. However, cdc35 cells are only found as yeast-like cells, forming grape-like shapes (Fig. 7).

**Discussion**

In common with most insects, the fruit fly D. melanogaster is very resistant to microbial infection. This is due to the presence of the physical barriers, formed by the external cuticle as well as the chitinous membranes of the gut and the trachea. In addition, Drosophila maintains a low internal pH hostile to many pathogens. Finally, a plethora of inducible immune reactions in response to invasion of a pathogen will lead to the secretion to high concentrations of AMPs in the hemolymph (38). However, a growing body of work indicates that D. melanogaster can be infected by various pathogens through natural routes or by injections, and thus this genetically tractable organism can serve as a model to dissect host-pathogen interactions, without the overlying complexities of complement and Ab responses (38, 42).

We used thoracic injection of adult wild-type Drosophila to evaluate the use of the fruit fly as a host model for the human opportunistic fungal pathogen C. albicans. This strategy allowed us to successfully infect Drosophila. The mode of infection used (i.e., pricking through the cuticle) overcomes limitations encountered with natural infection routes (e.g., size of the organisms with C. elegans (11)) and thus broadens the spectra of fungi that might be studied in Drosophila.

In Drosophila, C. albicans undergoes morphological differentiation in a manner similar to what occurs during infection of mammalian hosts (43). This morphological transition from yeast to pseudohyphae occurs in vitro and in vivo in response to a range of environmental cues such as temperature above 35°C, high pH, or the presence of serum. Because our infection experiments were performed at 30°C (the nonpermissive temperature of the Toll-thermosensitive allele), it is not possible to attribute the pseudohyphal differentiation of C. albicans in Drosophila to elevated temperature but rather to factors associated with the host environment such as pH, ion distribution, or intercellular contacts.

C. albicans survives in a wide variety of mucosa and can cause diseases in different body locations, displaying a versatility far greater than most other commensal microorganisms. These abilities can be categorized as virulence traits. Genetic approaches have been used to try to unravel the virulence traits contributing to C. albicans pathogenesis (6). To do so, C. albicans carrying deletion in specific genes are most frequently tested in acute-lethality mouse models. We have used three such C. albicans mutant strains to infect Drosophila. Our work shows that C. albicans genes essential for infection in mammalian models are also critical to successfully infect wild-type Drosophila, validating the use of this insect model. In addition, Drosophila Toll mutants revealed that the rank order of virulence of these C. albicans mutants, considering both the lethality and the rate of killing, is similar in the Toll mutants and in mouse models. Interestingly, the rank order of virulence of the mutant C. albicans strains followed the ability of these strains to form hyphae. Hence, these data support the common view of the importance of morphological differentiation for virulence. However, decreased virulence has also been associated with gene deletions not affecting hyphal formation (44, 45). In addition, Odds et al. (46) established that injection of very high numbers of a given C. albicans strain can lead to pathologically significant tissue burdens independent of hyphal formation. Our experiments showed that tissue invasion is not solely dependent on morphological differentiation, because the cdc35 mutant is able to invade tissues in the Drosophila Toll mutants, even though this

### FIGURE 7

Morphology of C. albicans in Toll transheterozygotes. Females Toll mutant flies infected with C. albicans SC5314 were crushed 12–24 h postinfection in Drosophila Ringer’s solution and observed under light microscopy.
strain does not undergo yeast-to-hyphae transition. This is a particularly interesting observation, because infection in the Drosophila Toll mutants allows for the uncoupling of hyphal differentiation and tissue proliferation. The observed virulence of the cdc35 mutant strain in Toll mutant flies indicates that deletion of the CDC35 gene strongly hampers, but may not totally block the virulence of C. albicans, which underscores the fact that infection with C. albicans of Drosophila Toll mutants—due to their higher susceptibility—revealed more subtle effects of specific mutations in C. albicans compared with infection of wild-type flies and, by extension, to models of immunocompetent mice. This may not be surprising in view of the facts that virulence studies with this strain were performed in an immunocompetent mouse model (28), that the cdc35 strain is able to colonize the marine vaginal mucosa for up to 10 days (28), and that this strain is able to induce macrophage death, albeit at a slower rate than a wild-type C. albicans strain (47). C. albicans is a commensal, hence, its virulence potency although present in immunocompetent hosts, is silent and does not induce infection. Consequently, our immunosuppressed fly model is all the more relevant and should prove useful for the study of C. albicans virulence determinants.

Infection of Toll mutants with the C. albicans mutant strains tested resulted in a similar threshold of ~40% survival, significantly higher than the survival rate obtained with the SC5314–H11011 strain. This may result from defects inherent to the mutant strains, which are also the bases for their reported virulence defects in systemic infection models (28–30). Interestingly, it was demonstrated that the SAP4–6 genes are not essential for mucosal infection (48, 49), and that clu4 mutants are very resistant to killing by macrophage (47) and behave very similarly to wild-type C. albicans in an in vitro mouse endothelial cell model (39). Thus, the differences in virulence observed in our fly model with these mutant strains may reflect defects in elements also needed for systemic infection in mice. The better survival of the Toll transheterozygotes when infected with our C. albicans mutants may also reflect the ability of the flies to induce defense mechanisms that have little effect on the fast proliferating wild-type SC5314 strain—because their onset is too slow and/or because this strain has capacities to overcome them—but can alter the propagation of slower progressing C. albicans strains. Indeed, the small but detectable levels of metchnikowin may allow the mutant flies to prevent the C. albicans mutants to proliferate beyond a certain point, thus explaining the limitation in the effect on survival of the C. albicans mutants, effect on SC5314 being hampered by the rapid proliferation in the flies of this latter strain.

Distinct mammalian TLRs are involved in the activation of immune cells by various pathogen-specific patterns (50). In particular, the TLR2 receptor was shown to relocalize to phagosomes in murine macrophages upon phagocytosis of zymosan (51, 52). TLR2 and TLR4 were shown to play an important role in signaling of immune response pathways to the fungi Aspergillus nidulans in macrophages, B cells, and T cells (52, 53). In addition, TLR4 was also involved in the immune response to the fungal pathogen Cryptococcus neoformans (54). Finally, TLR4 was recently shown to play a role in the murine immune response to C. albicans (55). These data, together with our identification of the critical role of the TLR receptor in Drosophila immune response against C. albicans, support the idea that TLRs may contribute to the innate immune response to C. albicans in mammals.

The uncovering of a high degree of conservation of components of the innate immunity between mammals and Drosophila renders the latter a very attractive model to study various host-pathogen interactions. Our work establishes the grounds for the use of Drosophila in studying the interplay between C. albicans and the host innate immune response. We showed that C. albicans genes important for virulence in mammalian models are also important for infecting Drosophila and that the Toll pathway, conserved in higher eukaryotes, is essential for the resistance of Drosophila to C. albicans. Our pathogenesis model, in which both the pathogen and the host are genetically tractable, will undoubtedly provide a critical tool to decipher the function of C. albicans virulence factors as well as host response against them, issues at the core of host-pathogen interactions.

Acknowledgments

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References


