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Differential Adherence of Hydrophobic and Hydrophilic *Candida albicans* Yeast Cells to Mouse Tissues

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Using an ex vivo binding assay, we previously demonstrated that yeast cells grown at 37°C display binding specificity in mouse spleen, lymph node, and kidney tissues. In spleen and lymph node tissues, binding was predominantly in regions rich in macrophages. Here, we tested the possibility that hydrophobic and hydrophilic cells bind differentially to host tissues. Hydrophobic and hydrophilic yeast cells of four *Candida albicans* strains were incubated for 15 min at 4°C with cryostat sections of organs that had been rapidly frozen after removal from BALB/cByJ mice. Unattached cells were removed by washing, and the sections were examined. Hydrophobic cells bound diffusely and abundantly to all tissues, while hydrophilic cell attachment was restricted to specific sites. For example, hydrophobic cells bound to the white and red pulp and the marginal zones in spleens, whereas hydrophilic cells attached primarily to the marginal zones. Hydrophobic yeast cells attached throughout lymph node tissue including paracortical areas, but hydrophilic cell attachment occurred primarily at the subcapsular and trabecular sinuses. EDTA inhibited the adherence of hydrophilic cells but not hydrophobic cells to mouse tissues. Hydrophobic *C. albicans* strains displaying similar levels of hydrophobicity differed quantitatively in their levels of attachment to kidney and spleen tissues, confirming our earlier observation that surface hydrophobicity is not the sole determinant in adherence to host cells. Other studies have shown that hydrophobic and hydrophilic cells display different virulence characteristics related to their surface properties and that hydrophobic cells are more virulent than hydrophilic cells. Taken together, the present results suggest that the enhanced virulence of hydrophobic cells over hydrophilic cells may be due, in part, to the potential of hydrophobic cells to bind throughout various organs following clearance from the bloodstream.

Nearly all tissues of the human body are susceptible to invasion by *Candida albicans* (27). Hydrophobic yeast cells have been shown to be more virulent than hydrophilic cells in mice (1). However, the contribution of yeast cell surface hydrophobicity (CSH) to fatal, disseminated candidiasis is not known. We and others have shown that CSH enhances the ability of *C. albicans* to adhere to epithelial tissue (for a review, see reference 12). In addition, hydrophobic cells are not killed as rapidly as hydrophilic cells by polymorphonuclear neutrophils (1). A similar observation for hydrophobic versus hydrophilic conidia of *Aspergillus* and *Rhizopus* species has been made by others (for a review, see reference 6). These results suggest that expression of surface hydrophobicity could contribute to successful colonization of host tissues.

Whether *C. albicans* is hydrophobic or hydrophilic as a commensal of the human host and converts to the alternate surface phenotype during parasitism is unknown. Previous studies demonstrated that *C. albicans* is typically hydrophilic when grown at 37°C (13, 16), but conversion from surface hydrophilicity to hydrophobicity can occur rapidly. Under certain conditions, such as inoculation into fresh growth medium or into tissue culture medium, the hydrophilic cells become hydrophobic within 60 min (9). De novo synthesis of hydrophobic surface proteins does not appear necessary for the surface conversion. Hydrophilic cell walls possess hydrophobic proteins which can easily be exposed by treatment with dithiothreitol (15). Once yeast cells become hydrophobic, they may rapidly produce germ tubes and become invasive (19, 25).

Using a modified ex vivo tissue adherence assay, we recently demonstrated that yeast cells grown at 37°C bind predominantly to areas of lymph node and spleen tissue that are rich in macrophages (5). Such yeast cells may be inhibited from growth in these tissue sites because of the antifungal properties of the phagocytes. In the present study, the ability of hydrophobic cells to bind to murine tissues in the ex vivo assay was compared with that of hydrophilic cells in order to determine whether the enhanced virulence of hydrophobic cells could be associated with differential tissue-binding characteristics. The results demonstrate that hydrophobic cells are capable of binding abundantly to all tissues and to areas of tissue essentially devoid of macrophages. Hydrophilic cells bound to these tissues in patterns similar to those described in our earlier report (5) for yeast cells grown at 37°C.

MATERIALS AND METHODS

Organisms and growth conditions. Four isolates of *C. albicans* were used. *C. albicans* isolate LGH1095, originally obtained as a blood culture of a septicemic patient, has been used extensively as the standard laboratory strain in previous studies (1, 9, 13, 16). Isolates Ca222, Ca9938, and Ca312

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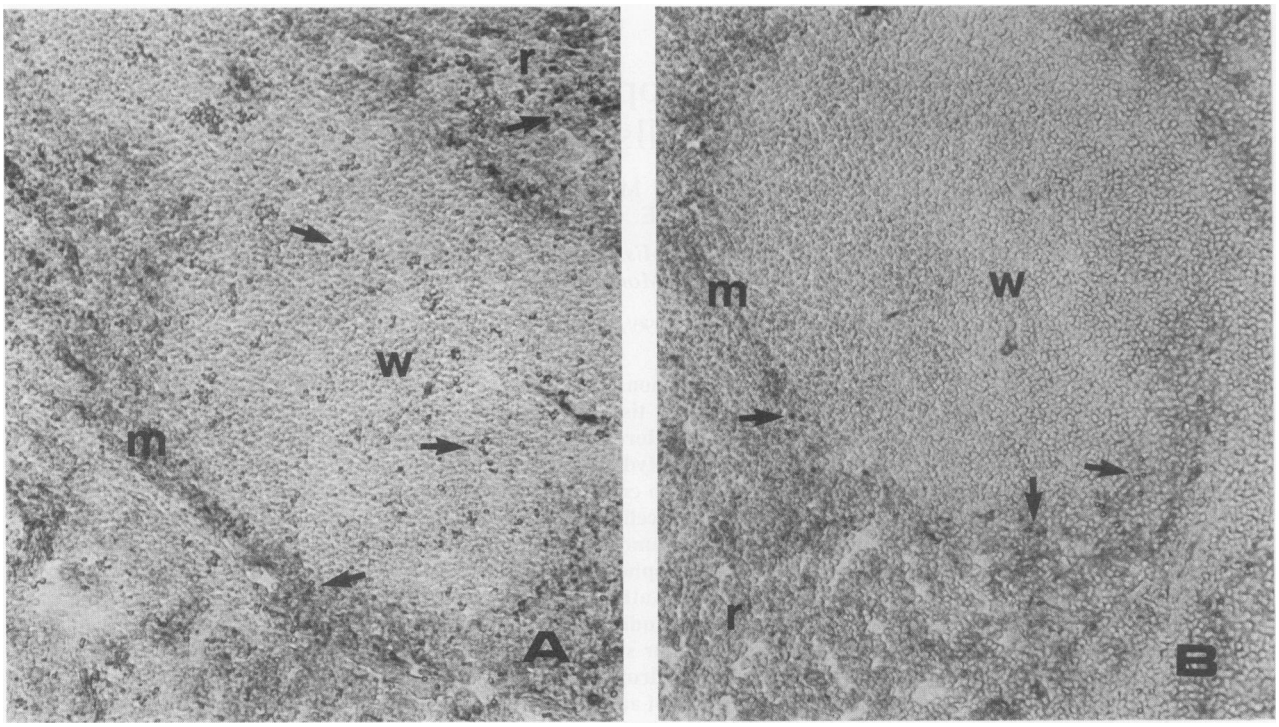

FIG. 1. Binding patterns of hydrophobic (A) and hydrophilic (B) yeast cells of *C. albicans* isolate Ca222 to mouse spleen tissue ex vivo. A suspension of yeast cells was placed on cryostat sections of mouse spleen tissue and incubated for 15 min. The tissues were fixed with glutaraldehyde, and the nonattached cells were washed off. Hydrophobic cells bound throughout splenic tissue (arrows in panel A point to some of the cells in white and red pulp and in the marginal zone). As seen in our earlier study (5), hydrophilic cells, which were obtained by growth at 37°C, attached primarily to the marginal zone (panel B, arrows). Abbreviations: w, white pulp; m, marginal zone; r, red pulp. Cells grown at 37°C (hydrophilic) are larger than those grown at room temperature (hydrophobic) (14). Magnification, ×100.

were used in our previous ex vivo tissue adherence study (5). Isolate A9 and the mutant A9V10 have been described elsewhere (30). All isolates were stored as part of our stock collection at −70°C and subcultured onto Sabouraud dextrose agar (Difco Laboratories, Detroit, Mich.) at 37°C for 48 h prior to use in experiments. To prepare organisms for the ex vivo adherence experiments, yeast cells were grown in glucose (2%)–yeast extract (0.3%)–Bacto-Peptone (1.0%) broth (GYEPB) at 24 or 37°C. For most experiments, the cells were grown for 24 h in 25 ml (at 24°C) or 75 ml (at 37°C) of GYEPB contained in 125-ml Erlenmeyer flasks with rotation (160 rpm; Incubator Shaker; New Brunswick Scientific Co., Inc., Edison, N.J.). The cells were then subcultured twice at 24-h intervals and used after a final incubation period of 24 to 26 h (stationary phase). At the end of the final incubation period, yeast cells were washed three times in sterile, ice-cold distilled water and kept pelleted under Dulbecco's phosphate-buffered saline (Sigma Chemical Co., St. Louis, Mo.) at 0 to 4°C for no more than 2 h. The effects of growth medium and phase on adherence to tissues ex vivo and on expression of CSH have been described elsewhere (5, 9, 16).

Hydrophobic microsphere assay. CSH levels of *C. albicans* yeast cells were determined by the hydrophobic microsphere assay which has been described in detail elsewhere (8, 10, 13). Briefly, equal volumes (100 μl) of yeast cells (2×10^6/ml) and hydrophobic (i.e., low-sulfate), blue polystyrene microspheres (diameter, 0.801 μm; ca. 9×10^8 microspheres per ml), each suspended in sodium phosphate buffer (0.05 M, pH 7.2), were placed into acid-washed glass tubes (12 by 75 mm), equilibrated to room temperature for 2 min, and vigorously mixed on a flat-top vortexer (Maxi-Mix; Thermolyne, Dubuque, Iowa) for 30 s. Preliminary studies have shown that microspheres with a diameter of 0.801 μm provide results comparable to those obtained with 0.845-μm microspheres, which we used in some of our earlier studies (8–11, 13). The percentage of cells (at least 100 cells counted per sample) with three or more attached microspheres, as determined by bright-field microscopy, was considered the CSH level of the population. This level is an expression of the percentage of cells which are hydrophobic. The difference of CSH value from 100% is the hydrophilic level of the cell population. Previous work has shown that the CSH levels obtained with the hydrophobic microsphere assay are similar to those obtained with an aqueous phase-to-hydrocarbon assay (13).

Ex vivo tissue adherence assay. The ex vivo adhesion assay used for measuring *C. albicans* binding to host tissues was described in our previous report (5). Briefly, 10- to 12-week-old, female BALB/cByJ mice were injected with 100 μl of leuconyl blue (40% in saline; BASF, Holland, Mich.) 5 min prior to sacrifice. Unfixed cryostat sections (10 μm) of mouse spleens, lymph nodes, and kidneys previously embedded in Tissue Tek OCT compound (Miles, Elkhart, Ind.) and rapidly frozen on dry ice were cut and allowed to dry for 15 to 60 min at room temperature. Washed, stationary-phase yeast cells were suspended to 2.0×10^8/ml in Dulbecco's modified Eagle medium (DMEM) with HEPES (*N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid) (10 mM; Mediatech, Washington, D.C.) and 5% defined bovine calf

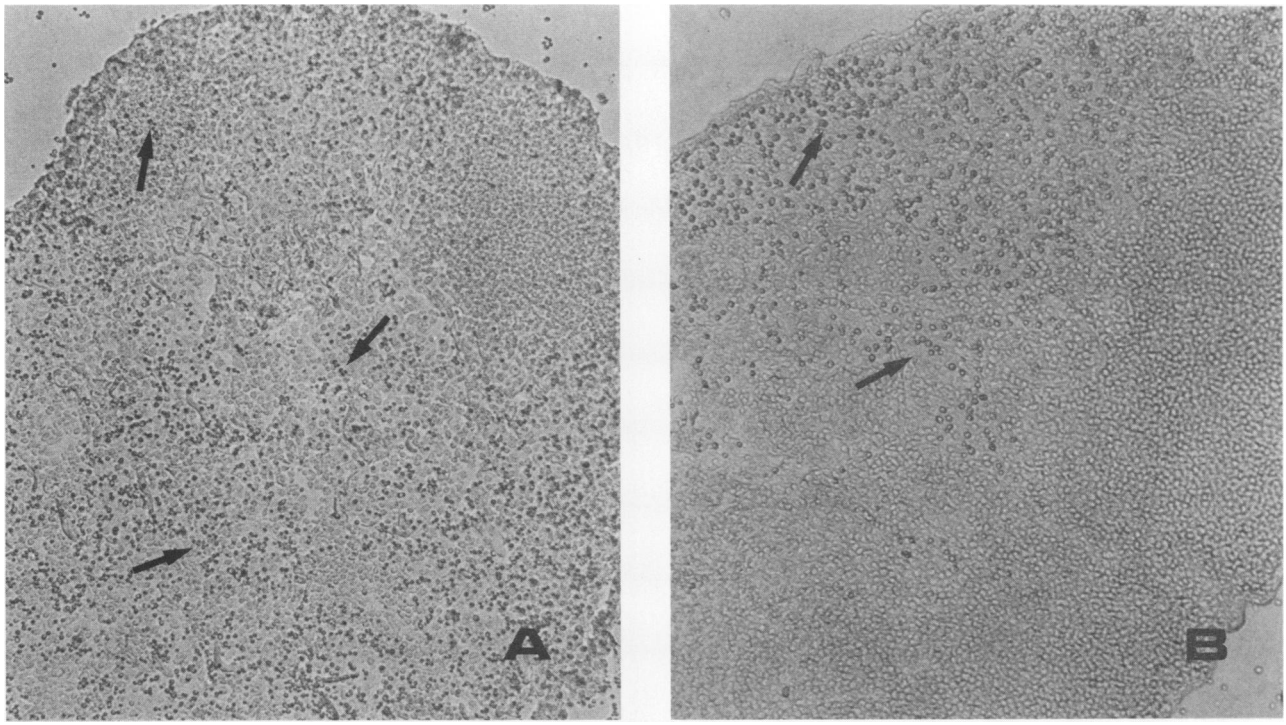

FIG. 2. Binding patterns of hydrophobic (A) and hydrophilic (B) yeast cells of *C. albicans* isolate Ca222 to mouse lymph node tissue ex vivo. The method is described in the legend to Fig. 1. In lymph node tissue, attachment of hydrophobic cells included the subcapsular and trabecular sinuses and paracortical areas. Hydrophilic cells attached only to the sinuses. The arrows point to a few of the many yeast cells attached to this tissue. Magnification, ×100.

serum (Hyclone, Logan, Utah). Henceforth, this medium is referred to as CDMEM. Each tissue section was overlaid with 100 μl of the yeast cell suspension and incubated with rotation (75 rpm, S/P Rotator V; Baxter Healthcare Corp., McGaw Park, Ill.) for 15 min. Preliminary studies demonstrated that the incubation temperature (4, 22 to 24, or 37°C) did not influence adherence of yeast cells to tissues. However, in order to minimize cell wall changes that could occur during the incubation period at 37°C (11), the tissues were incubated at either 4°C or 22 to 24°C. After incubation, the tissue sections were fixed in 1.5% glutaraldehyde (Fisher Scientific, Fair Lawn, N.J.) for 35 min to 16 h and subsequently rinsed gently several times in cold tap water. The distribution and abundance of adherent yeast cells were determined by bright-field microscopy.

To test the effects of EDTA on adherence by hydrophobic and hydrophilic cells to tissues, Hanks' balanced salt solution without calcium, magnesium, and serum (HBSS) was substituted for CDMEM. Yeast cells were suspended in HBSS with or without EDTA (10 mM; Sigma) prior to the binding assay.

RESULTS

Effects of CSH on adherence to tissues ex vivo. All wild-type isolates of *C. albicans* displayed CSH levels greater than 70% when grown at 24°C and less than 10% when grown at 37°C. For all tissues and isolates of *C. albicans* that we tested, hydrophobic yeast cells (high CSH level) attached in greater numbers than hydrophilic cells (low CSH level). Unlike hydrophilic cells, which displayed specificity for sites of attachment with each particular tissue, hydrophobic cells were generally more diffusely distributed (Fig. 1). In spleens, hydrophobic cells were distributed throughout the white pulp, marginal zones, and the red pulp (Fig. 1A), whereas hydrophilic cells attached primarily to the marginal zones of the white pulp (Fig. 1B). In lymph nodes, hydrophobic cells bound throughout the tissue including the paracortical regions (Fig. 2A), but hydrophilic cells attached primarily to the subcapsular and trabecular sinuses (Fig. 2B). In kidneys, the hydrophobic and hydrophilic cells bound to the nephrons and to the arterioles, but the hydrophilic cell population bound in lower numbers (Fig. 3). These general patterns of hydrophilic and hydrophobic cell binding to the various tissues were obtained for all four isolates of *C. albicans*. Variable and unpredictable attachment to the glass slides by hydrophobic cells was also seen, but tissue adherence by these cells was consistent.

Effects of CSH level and growth temperature on tissue adherence. The levels of CSH and adherence to spleen and kidney tissues were quantitatively determined for four strains of *C. albicans*. This analysis confirmed that hydrophilic cells adhered in lower numbers than hydrophobic cells and that hydrophilic cells attached in splenic tissue predominantly to the marginal zones (Table 1). The results also demonstrate that strains expressing similar, high levels of CSH (i.e., greater than 70%) may exhibit different levels of adhesion to tissues (compare strains Ca222, Ca312, and A9 in Table 1).

Growth temperature does not appear to dictate patterns of cell adhesion to tissues. When the mutant A9V10 and its parental wild-type A9 were grown at 37°C, their respective

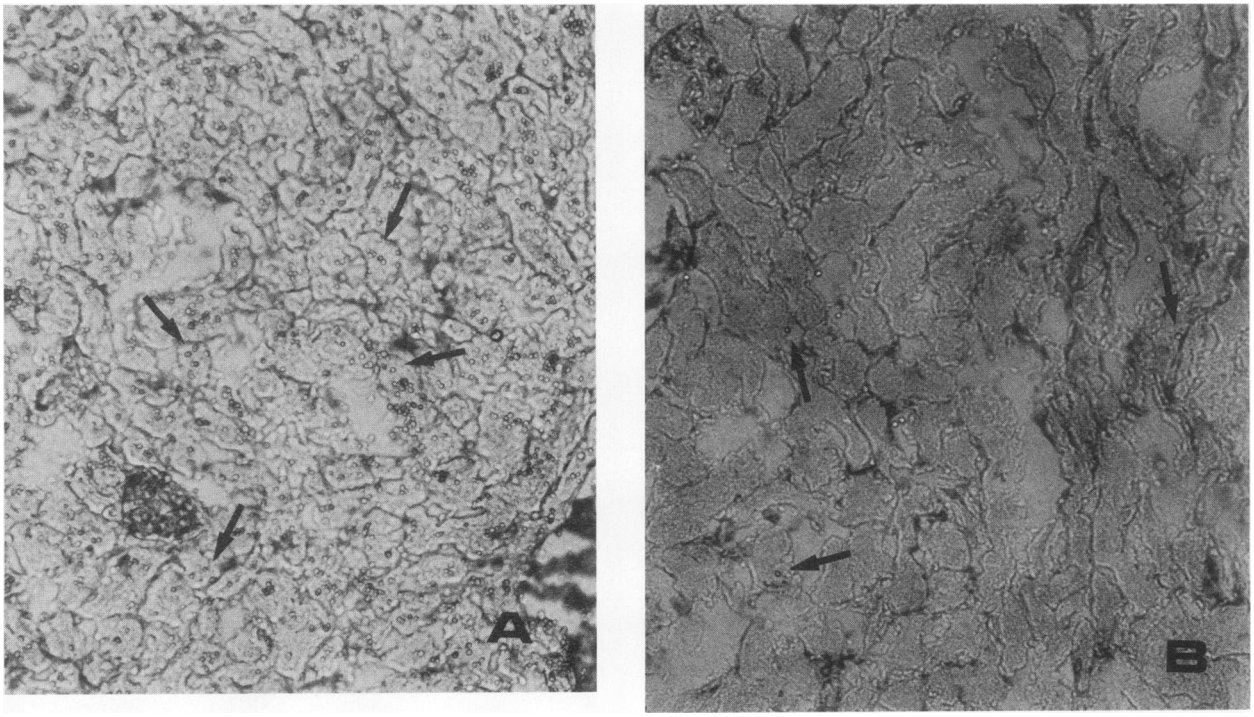

FIG. 3. Binding patterns of hydrophobic (A) and hydrophilic (B) yeast cells of *C. albicans* isolate Ca222 to mouse kidney tissue ex vivo. The method is described in the legend to Fig. 1. The attachment patterns of hydrophobic and hydrophilic cells were similar, but hydrophobic cells bound in greater numbers. The arrows point to some of the yeast cells attached to the tissue. Magnification, ×100.

levels of CSH were substantially different (Table 1). The patterns of tissue adherence were also different, with the more hydrophobic strain (A9V10) attaching to spleen and kidney tissues in greater numbers than strain A9 and in patterns similar to those of cells from wild-type hydrophobic (24°C) cultures.

Effects of EDTA and serum on yeast cell adherence. When hydrophobic and hydrophilic yeast cells of *C. albicans* isolate LGH1095 were suspended in HBSS instead of CDMEM, their respective patterns of adherence to mouse tissues did not change (data not shown). This result indicates that bovine calf serum is not needed for adherence by either hydrophobic or hydrophilic cells. The addition of EDTA to HBSS prevented binding of hydrophilic cells to all tissues tested (kidney, spleen, and lymph node) but had no effect on hydrophobic cells (data not shown).

TABLE 1. Adherence of *C. albicans* strains grown at 24 and 37°C to mouse spleen and kidney tissues

Strain	Growth temp (°C)	CSH (%)	Total *C. albicans* cells bound to tissue in 10 fields (SD)[a]			
			Spleen			Kidney
			Marginal zone[b]	Red pulp	White pulp	
LGH1095	24	73	711 (75)	559 (50)	573 (267)	743 (64)
	37	0	46 (27)	3 (3)	2 (2)	4 (2)
Ca222	24	90	1,329 (219)	1,387 (388)	1,364 (293)	1,340 (244)
	37	2	26 (18)	2 (2)	1 (1)	5 (5)
Ca312	24	96	938 (129)	689 (230)	771 (139)	1,191 (236)
	37	0	37 (5)	2 (1)	0 (1)	4 (2)
A9	24	87	1,624 (423)	1,425 (284)	1,389 (286)	1,717 (292)
	37	0	16 (7)	2 (2)	0 (0)	1 (1)
A9V10	24	99	1,896 (391)	1,417 (323)	1,694 (406)	1,619 (354)
	37	76	260 (82)	218 (52)	69 (37)	378 (60)

[a] Mean of quadruplicates obtained by counting total *C. albicans* cells bound to tissues in 10 fields (5 randomly selected from each of 2 tissues). Field size was 80 by 200 μm when yeast CSH was low. When yeast CSH was high, field size was 80 by 80 μm and the values were multiplied by 2.5.

[b] Fields were selected from among marginal zones binding one or more *C. albicans* cells.

DISCUSSION

The ex vivo tissue-binding assay is based upon an assay originally used in studies of leukocyte homing in vivo (4, 22, 29). This approach has been useful in defining a variety of adhesion molecules involved in leukocyte-endothelial cell interactions. These include the MEL-14 antigen, LPAM-1, MAC-1, LFA-1, and the vascular addressins in mice and DREG/LEU-8/LAM-1, VLA4, and vascular addressins in humans (18; for a review, see reference 2). Korhonen and colleagues (20, 21, 24) have also used a similar assay to investigate *Escherichia coli* adhesins involved in attachment to urinary tract tissues.

On the basis of the results of the ex vivo assay, hydrophobic yeast cells are able to bind to host tissues diffusely and abundantly. This is not surprising, since hydrophobic interactions occur at relatively long ranges, and yeast cell surface-hydrophobic molecules may not require specific tissue receptors to mediate adhesion (for reviews, see references 17 and 23). Attachment of hydrophilic yeast cells of *C. albicans* occurred predominantly at specific regions of each tissue. Specifically, hydrophilic cells bound to regions rich in macrophages (5). This result indicates that hydrophilic yeast cell adherence involves specific adhesin-receptor interactions. Hydrophobic cell attachment to splenic tissue, however, was not primarily limited to the macrophage-rich marginal zones but occurred as well in the white and red pulp. If these adherence patterns occur in vivo, then the ability to bind to tissue areas free of macrophages may allow hydrophobic cells to be more successful than hydrophilic cells in colonizing host tissues following clearance from the bloodstream. This hypothesis is consistent with previous findings that hydrophobic cells are more virulent than hydrophilic cells in mice (1).

Recent reports have demonstrated that several other attributes of *C. albicans* which contribute to enhanced virulence are affected by growth temperature. These include production of exoenzymes (14), expression of specific adhesins (7), and sensitivity to toxic substances (14). For many of the *C. albicans* strains used in the present study, growth temperature was used to influence the level of CSH. However, growth temperature is not responsible for the difference in adherence levels seen between hydrophobic and hydrophilic cells. When grown at 37°C, the mutant strain A9V10 was hydrophobic and adhered throughout the tissues and in substantially greater numbers than the hydrophilic wild-type A9 strain also grown at 37°C (Table 1).

The results from strains Ca312 and Ca222 grown at 24°C (Table 1) demonstrate, in agreement with an earlier observation (11), that a direct correlation between CSH levels and adherence to epithelial cells is not obtainable when a comparison is made between different strains (11). This is likely due to differences in expression and cell wall concentration of the multiple yeast cell surface factors (e.g., adhesins, fibrils, and integrin receptors) that influence *C. albicans* adherence to host tissues (3, 12, 19). However, for a given strain, there is a positive correlation between CSH levels and attachment to epithelial cells (11). In the present experiments, this correlation may also be true between strain A9 and the mutant strain A9V10. For these strains, an increase in CSH level corresponded with an increase in adherent cells to splenic tissue.

Attachment of hydrophilic cells to mouse tissues ex vivo was inhibited by EDTA, which is consistent with the role of electrostatic forces in adhesin-receptor interactions (12, 23) and the contribution of divalent cations to cell-cell adherence. Other investigators have shown that Ca^{2+} (31), Mg^{2+} (28), or both (26) participate in adherence of leukocytes to host cells. Hydrophobic yeast cell adherence to mouse tissues, on the other hand, was unaffected by EDTA. These results support the possibility that hydrophobic interactions, which can occur at long ranges (distances up to 10 nm [17]), can facilitate specific adhesin-receptor interactions, which occur at short ranges (less than 2 nm), by bringing cognate surface structures closer than would occur without hydrophobic interactions. Thus, as seen in the present study, hydrophobic cells, which presumably also express specific adhesins (11, 15, 19), may be more likely to attach to host tissue sites during dissemination. In addition, preliminary results indicate that hydrophobic cells seed kidney tissues and produce germ tubes within 1 h after intravenous inoculation into mice, whereas hydrophilic cells remain as yeast forms (data not shown). This observation correlates with an earlier study showing that hydrophobic cells germinate more rapidly than hydrophilic cells (9). Furthermore, hydrophobic cells are less susceptible to killing by phagocytes (1). These various findings support the concept that hydrophobic cells are excellent candidates for initiating invasive disease.

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