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MINIREVIEW

Candida albicans-Endothelial Cell Interactions: a Key Step in the Pathogenesis of Systemic Candidiasis▽

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Candida albicans is a normal commensal organism of the oral cavity, gastrointestinal tract, and vagina. Under certain circumstances, *C. albicans* is capable of causing host damage (or disease) leading to oral, vaginal, cutaneous, or systemic candidiasis. The latter is a serious infection with a high mortality range of 33% to 54% and high morbidity in those who survive (76). In fact, in recent years, systemic candidal infections have become the fourth most frequent cause of nosocomial bloodstream infections in the United States, giving rise to an enormous associated personal and economic cost (79). Systemic candidiasis involves the hematogenous spread of *C. albicans* to multiple organs, including the brain, kidneys, heart, liver, and lungs (62). Histologically, infection of these organs is characterized by ramifying candidal hyphae and accompanying yeast forms that produce multiple necrotic nodules or abscesses that result in extensive organ damage leading to organ failure. Risk factors for systemic candidiasis include neutropenia, intravascular catheters, hemodialysis, total parenteral nutrition, abdominal surgery, burns, broad-spectrum antibiotics, and corticosteroids (63). Systemic innate immune responses by phagocytic cells, particularly neutrophils and macrophages, appear to play a critical role in the host defense against systemic *Candida* infections, and consequently, the majority of candidal infections occur in patients with neutropenia or defects in neutrophil or macrophage function (5, 55).

MORPHOGENETIC CONVERSIONS AND *C. ALBICANS* VIRULENCE

C. albicans is a polymorphic organism that is capable of converting between yeast, pseudohyphal, and hyphal forms. The conventional view was that yeast forms were associated with commensal carriage, whereas hyphal forms were associated with disease. This was based on evidence showing that mutant forms of *C. albicans* that were locked into the yeast form were avirulent (50). However, this notion was challenged by Braun et al., who found that a *tup1*-deficient *C. albicans* strain that was constitutively pseudohyphal was avirulent in a murine model of systemic candidiasis (6, 7). Although the precise nature of the association between fungal morphogenesis and host invasion is a hotly debated topic (30), it is now widely accepted that it is the ability to undergo morphogenetic conversion, rather than the morphological form itself, that is the primary determinant of pathogenicity (71).

The dissemination of fungal organisms in systemic candidiasis starts with their entry into the bloodstream. Given the known risk factors for systemic candidiasis, this is most likely to occur in susceptible individuals by seeding from contaminated intravascular devices, by persorption of *C. albicans* across the gastrointestinal mucosa, by invasion of epithelially denuded surfaces, or via trauma or surgically related inoculation (4, 11, 34). Exit from the circulation is thought to occur by adhesion and then penetration into the endothelial lining of blood vessels, except possibly in the kidney, where direct adhesion to exposed extracellular matrix components within glomerular regions may occur (45). Animal studies suggest that candidal trafficking from the circulation into the tissues occurs rapidly (1, 38, 52). This review discusses the two critical steps in the migration of *C. albicans* cells from the circulation into the tissues, which are (i) candidal adhesion to endothelial cells lining the blood vessels and (ii) transmigration of *C. albicans* across the endothelium into the tissues.

ADHESION OF *C. ALBICANS* TO ENDOTHELIAL CELLS

During hematogenous dissemination of *C. albicans*, organisms must first adhere to the endothelial lining of blood vessels before transmigrating across the endothelium to invade the tissues. However, little is known about the mechanisms involved in either process. What is known is complicated further by conflicting evidence concerning the roles played by yeast, pseudohyphal, and hyphal forms of *C. albicans* and the role of morphogenetic change in the adhesion and transmigration processes.

There are currently two different theories as to how *C. albicans* adheres to the endothelium. The first theory proposes that cells must first undergo morphogenetic conversion to hyphal forms, which then bind to and damage the endothelial lining of blood vessels before undergoing transmigration from the circulation into the tissues. However, more recent data indicate a second possibility in which morphogenetic change is

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not necessary for *C. albicans* invasion of the tissues. In this scenario, yeast cells adhere to the endothelium and then transmigrate into the tissues without undergoing morphogenetic conversion.

The basis of the first theory is morphogenetic conversion of *C. albicans* to the hyphal form, and there are many lines of evidence to support this hypothesis. These include the observations that germination of *C. albicans* is necessary for the organism to damage endothelial cells (22, 67) and that substances that inhibit germination block *C. albicans*-induced endothelial cell damage (27). Moreover, the time course of candidal germination and germ tube elongation on endothelial cells parallels the time course of endothelial cell damage (20). Further evidence has come from experiments using genetically engineered forms of *C. albicans* with filamentation defects. The ability of these organisms to damage and invade endothelial cells is severely impaired compared to that of wild-type parent strains (64, 67).

Studies showing that germinated *C. albicans* cells exhibit much greater adherence to epithelial cells than do yeast forms (43) prompted suggestions that *C. albicans* adherence to endothelial cells might also be hypha dependent. Indeed, there is some evidence to suggest that germinated candidal forms exhibit greater endothelial cell adhesion than do yeast forms of *C. albicans* (66). However, it is also possible that yeast forms adhere to the endothelial surface, germinate there, and then penetrate and damage the endothelium during transmigration (22) or that yeast forms adhere and are then endocytosed before germinating within the endothelial cell to cause damage (64). Taken together, the data suggest that morphogenetic transformation is involved in endothelial cell adhesion but, more particularly, in the subsequent *trans*-endothelial cell migration.

Conversely, there is also evidence to suggest that morphogenetic change may not be necessary for *C. albicans* invasion, and this is the basis for the alternative hypothesis. In animal studies in which mice were intravenously inoculated with different mutant strains, Bendel et al. found that cells from a *C. albicans* mutant strain locked into the yeast form were able to leave the circulation and enter the tissues in greater numbers than those of the wild-type control (4). However, once cells were in the tissues, the ability of the wild-type strain to undergo hyphal transformation was associated with higher mortality, despite the lower fungal burden in the tissues than that with mutant yeast forms (4). Further evidence to support this theory has come from in vivo experiments investigating tissue invasion and damage, performed by Saville et al. using a genetically engineered strain of *C. albicans* (SSY50-B) (71). This study demonstrated that yeast cells are capable of extravasating from blood vessels into the tissues without undergoing morphogenetic change. However, once cells were in the tissues, morphogenetic conversion from yeast to hyphal forms was crucial in causing tissue damage leading to death.

Such observations have led to a hypothesis in which circulating yeast cells bind to the endothelium and then transmigrate into the tissues before undergoing the hyphal transformation that results in tissue damage. In support of this, *C. albicans* migration from the circulation is very rapid (80 to 90% migration within 5 min) (16, 52), whereas hyphal transformation and endothelial cell damage may take several hours (66). Furthermore, because of their more compact shape and size, yeast cells may be better adapted for free dissemination within the circulation (30). In addition, the emergence of *C. glabrata* and *C. parapsilosis* as contenders for the second most common cause of disseminated candidiasis, after *C. albicans* (68), indicates that the ability to form true hyphae may not be essential for tissue adhesion, invasion, and pathogenesis among *Candida* species (30).

CANDIDATE *CANDIDA* ADHESINS AND THEIR ENDOTHELIAL LIGANDS

The cell wall of *C. albicans* is composed primarily of an inner structural layer of β1,3- and β1,6-glucans and chitin (a β1,4-linked polymer of *N*-acetylglucosamine) and a matrix primarily consisting of proteins (mannoproteins) that are heavily glycosylated with mannose-containing polysaccharides, sometimes called mannans (Fig. 1) (57). These take the form of short, linear, O-linked mannan side chains that stabilize the protein in the cell wall (15) and large, highly branched N-linked mannans (12). It is this outermost layer that represents the first point of contact between *C. albicans* and the endothelium, although not at bud scars, where the components of the inner layers of the cell wall are exposed (26). Proteins and carbohydrates in these outer layers may have a number of functions, including the ability to act as adhesion molecules, and over recent years several *C. albicans* cell wall components with the potential to mediate adhesion to the endothelium have been identified (Table 1). These include proteins with integrin-like properties (reviewed in references 32 and 36), *Candida* agglutinin-like sequence (ALS) gene products (72, 84), and mannans (57).

Cell wall protein adhesin candidates. (i) Integrin $\alpha_M\beta_2$-like adhesin. Integrin analogues first gained interest in 1991, when Gustafson et al. found that adhesion of yeast forms of *C. albicans* to cultured monolayers of human endothelial cells was mediated in part by a candidal protein antigenically and structurally related to the leukocyte integrin $\alpha_M\beta_2$ (Mac-1, CD11b/CD18, CR3, or iC3b receptor) (9, 32, 48). They demonstrated the expression of the $\alpha_M\beta_2$-like molecule on yeast forms of *C. albicans* and showed that expression was increased by growth in 20 mM D-glucose, as opposed to 20 mM L-glutamine (32, 37). Furthermore, the adhesion of yeast forms of *C. albicans* to endothelial cells was significantly reduced by anti-$\alpha_M\beta_2$ antibodies or pretreatment of the *Candida* cells with purified iC3b. Expression of this ligand may be altered at different temperatures and in different morphogenetic forms of *C. albicans* (14, 28), and this may affect the ability of *C. albicans* to adhere to endothelium (80). $\alpha_M\beta_2$ has many different ligands, including iC3b, fibrinogen, factor X, urokinase receptor, CD14, CD23, CD54 (ICAM-1), CD102 (ICAM-2), CD242 (ICAM-4), heparin, haptoglobin, kininogen, and various microbial proteins (33). Of these molecules, only ICAM-1 and -2 are widely expressed on endothelial cells, although CD14 was recently identified on primary, but not passaged, cultures of human umbilical vein endothelial cells (49). There are no data on the role of CD14, CD102, or CD242 as a possible endothelial ligand for *C. albicans* adhesion, but Yokomura et al. (82) have shown that anti-CD54 monoclonal antibodies can partially inhibit the adhesion of yeast forms of *C. albicans* to rat pulmonary artery

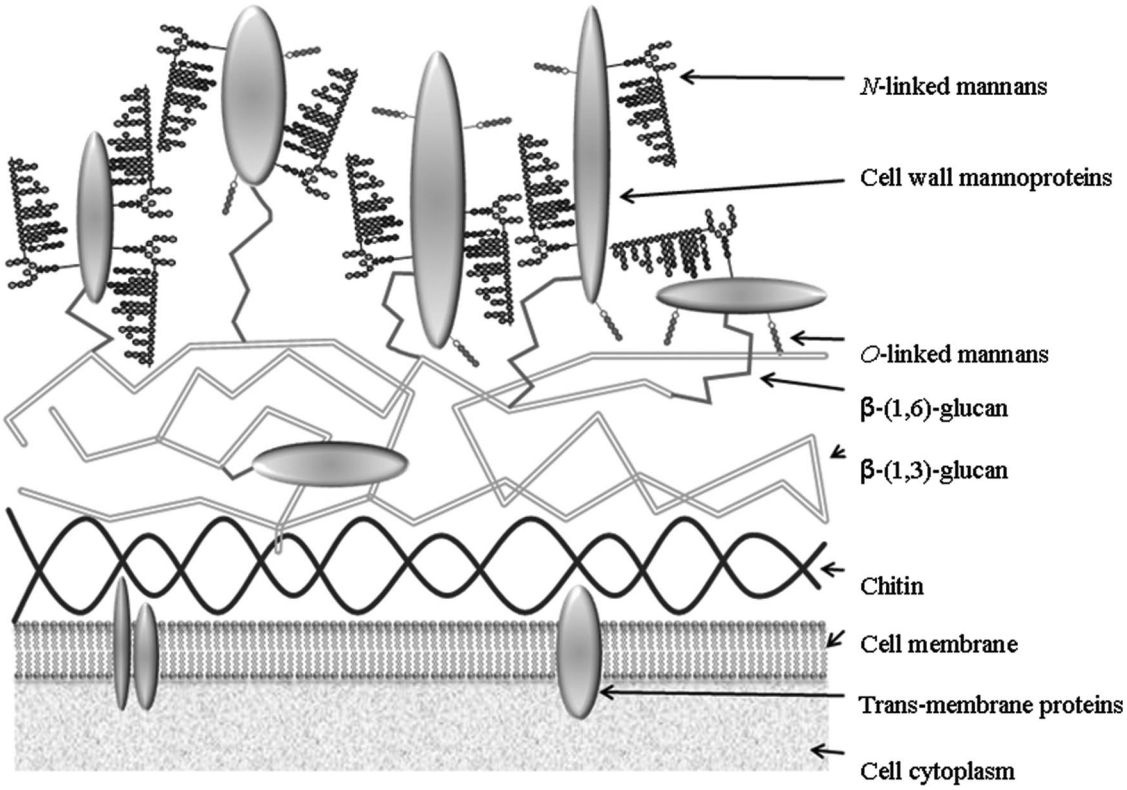

FIG. 1. Cartoon of *Candida* cell wall structure.

endothelial cells in vitro and significantly prolong the survival of rats injected intravenously with *C. albicans*. In certain circumstances, it is also possible that $\alpha_M\beta_2$ ligands such as fibrinogen, heparin and iC3b could in turn bind to endothelial cells and act as an intermediary in *Candida*-endothelial cell adhesion.

TABLE 1. *Candida albicans*-endothelial cell adhesion molecules

C. albicans adhesin	Morphogenetic expression[e]	Endothelial ligand(s) (potential ligand)	Reference
$\alpha_M\beta_2$ (Mac-1; also called CD11b/CD18)	Y + PH[a]	CD54, CD102, CD14	9, 32, 48, 82
$\alpha_v\beta_3$ (CD51/CD61)	Y + H[c]	PECAM-1 (CD31)	70, 73
$\alpha_v\beta_5$	Y + H[d]	?	70, 73
Als1	Y + H[c]	?	24, 25, 72, 83
Als2	Y + H[a]	?	86
Als3	H	N-cadherin	65, 83
Als4	Y + H[a,d]	?	86
Als5[b]	Y	?	72, 84
Als6[b]	Y	?	72, 84
Als7[b]	Y	?	84
Als9	Y	?	85
N-linked mannosyl residues	All forms	MR	58, 81
O-linked mannosyl residues	All forms	TLR-4	3, 59, 60, 74
Phospholipomannan	All forms	TLR-2	42
β-Mannosides	All forms	Galectin-3	41

[a] Temperature-dependent expression.
[b] These molecules may be antiadhesive. See the text for further details.
[c] Increased expression on hyphae compared to yeast form.
[d] Decreased expression on hyphae compared to yeast form.
[e] Y, expressed on the yeast form; PH, expressed on the pseudohyphal form; H, expressed on the hyphal form.

(ii) Integrin $\alpha_v\beta_3$- and $\alpha_v\beta_5$-like adhesins. Two other integrin-like adhesins that may play a role in candidal adhesion to endothelium have been identified. They are homologs of the vitronectin-binding integrins $\alpha_v\beta_3$ (CD51/CD61) and $\alpha_v\beta_5$ (70, 73). Spreghini et al. (73) reported the expression of both of these adhesins on yeast forms of *C. albicans*, while Santoni et al. (70) showed that transformation to germ tubes was associated with a marked reduction in $\alpha_v\beta_5$-like integrin expression and an increase in $\alpha_v\beta_3$-like integrin expression. They also showed that adhesion of *C. albicans* germ tubes to endothelium was partially inhibited by anti-$\alpha_v\beta_3$ antibodies or an RGD sequence peptide. Heparin also inhibited germ tube adhesion, and when heparin treatment was combined with either anti-$\alpha_v\beta_3$ antibody or RGD peptide, the reduction in adhesion was greater still (70). More recently, it was shown that a candidal focal adhesion kinase-like protein may be involved in regulating yeast cell adhesion to endothelium via the $\alpha_v\beta_3$- or $\alpha_v\beta_5$-like adhesins (69) or in mediating intracellular signaling following ligand binding, much as focal adhesion kinase proteins are involved in integrin-mediated signaling in mammalian cells (10). Like its human counterpart, the candidal $\alpha_v\beta_3$-like adhesin has been shown to bind to vitronectin (70, 73), but other ligands for $\alpha_v\beta_3$ include CD31 (PECAM-1), fibronectin, fibrinogen, thrombospondin, von Willebrand factor, and RGD sequence peptides (33). CD31 is expressed by endothelial cells and could act as a direct ligand for *Candida* adhesion (39), while in certain circumstances it is possible that other ligands could act as a bridge in *Candida*-endothelial cell binding. Like

its human counterpart, the $\alpha_v\beta_5$-like adhesin on *C. albicans* also binds vitronectin and RGD peptides (70, 73), but $\alpha_v\beta_5$ lacks a known endothelial cell target ligand and thus may not be involved directly with adherence to the endothelium.

(iii) *ALS* gene family. The *ALS* (agglutinin-like sequence) gene family encodes a group of large glycosylphosphatidylinositol-linked cell surface glycoproteins (19). To date, eight *ALS* genes have been identified, including A*LS1* to *ALS7* and *ALS*9, all of which appear to have differing roles in adhesion and transmigration. These genes have gained particular interest recently, and evidence shows that *ALS1*-transformed *Saccharomyces cerevisiae* exhibits up to 100-fold greater adherence to endothelial cells (24, 25, 72), while Als1-deficient *C. albicans* hyphae exhibit reduced adhesion to endothelial cells (83). Similarly, *S. cerevisiae* transformed with *ALS3* shows increased adhesion (72), while Als3-deficient hyphal forms of *C. albicans* exhibit defective adhesion to endothelial cells (83). The loss of Als9 from yeast forms of *C. albicans* (85) or the loss of Als4 and decreased expression of Als2 from 1-hour-old germ tubes (86) also inhibit the adhesion of mutant *C. albicans* strains to endothelial cells. In contrast, mutational analysis has shown that deletion of *ALS5*, *ALS6*, or *ALS7* results in increased adhesion of yeast forms of *C. albicans* to endothelial cells, suggesting an antiadhesive role for these proteins (84). On the other hand, the protein Als5 has been found to mediate adhesion, along with Als1, when expressed in *S. cerevisiae* (72). To date, the only ligand for the *ALS* gene products that has been found on endothelial cells is N-cadherin, which binds to Als3 on *C. albicans* hyphae (65).

(iv) C4BP. The complement protein regulator C4b binding protein (C4BP) is able to bind to both yeast and hyphal forms of *C. albicans* and is predominantly localized at the tip of the germ tube on hyphae (53). This binding is normally regarded as a survival mechanism that inhibits complement activation and the attachment of opsonins to the microbial surface. However, it may also enhance the adhesion of yeast forms of *C. albicans* to endothelial cells. It is not clear if this enhancement of adhesion by the C4BP coating occurs by activating other *Candida* adhesins or by acting as a bridge.

Cell wall carbohydrate adhesin candidates. The outer cell wall proteins of *Candida* are heavily glycosylated with N- or O-linked mannosyl residues and have been found to be strongly involved in the recognition of *C. albicans* by the innate immune system (58). Indeed, some of these sugar residues provide conserved *Candida*-associated chemical signatures, known as pathogen-associated molecular patterns, by which the host is able to recognize the presence of the pathogen via host pattern recognition receptors (PRRs). In recent years, it has become apparent that specific host PRRs bind to and recognize specific mannosyl residues on *C. albicans*. For example, the mannose receptor (MR) recognizes and binds to N-linked mannosyl residues (81), while Toll-like receptor 4 (TLR-4) binds O-linked mannosyl residues (3, 59, 60, 74). Similarly, TLR-2 recognizes and binds phospholipomannan (42), and galectin-3 binds β-mannosides (41). As these mannosyl residues are part of the structure of the cell wall, they are expressed on all three different morphological forms of *C. albicans*. However, there is evidence to suggest that there are differences in the recognition of yeast and hyphae by TLR-2 and TLR-4 (77).

Although these PRRs are principally involved in the recognition of *C. albicans* by components of the host immune response, it is also possible that they are used by *C. albicans* to adhere to and transmigrate across the endothelial lining of blood vessels. Indeed, several studies have demonstrated the important role of the TLRs in experimental models of disseminated candidiasis. Netea et al. showed that TLR-4-defective C3H/HeJ mice have an increased susceptibility to disseminated candidiasis (60), and mice deficient in the universal TLR adaptor protein myeloid differentiation factor 88 (MyD88) are extremely susceptible to *C. albicans* infection (78). However, it has also been shown that TLR-4-deficient mice are more resistant to disseminated *Candida* infection (3). This is also the case for TLR-2-deficient mice, which have also been shown to be more resistant to disseminated candidiasis (60). However, the majority of the literature on knockout mice and disseminated candidiasis looks at susceptibility to infection and correlates it with the immune response without focusing on receptor expression on endothelial cells. To date, endothelial cells have been shown to express a number of PRRs, including the MR, TLRs, and galectins. The MR was the first receptor on the surfaces of macrophages to be described as a mannan receptor, and it recognizes oligosaccharides that terminate in mannose, fucose, and *N*-acetylglucosamine. It is also expressed on subtypes of dendritic cells and endothelial cells from certain vascular beds, including human dermal microvascular endothelial cells but not human umbilical vein endothelial cells (31). So far, 10 TLRs have been found, of which 7 or 8 are expressed on unstimulated endothelial cells (23). However, upon stimulation with proinflammatory cytokines, all 10 TLRs are expressed. Perhaps most importantly for interactions with *C. albicans*, endothelial cells express TLR-2 and TLR-4 (61). TLR-4 is expressed constitutively at a higher level than that of TLR-2 by endothelial cells (17). However, the expression of both is significantly upregulated by stimulation with gamma interferon or bacterial lipopolysaccharide (18). It is also notable that the expression of TLR-2 on endothelial cells is strongly affected by the effects of flow on the endothelial cells (13). The galectins are a family of 15 carbohydrate binding proteins with high affinities for β-galactosides, extracellular glycoproteins, and glycolipids. So far, expression of galectin-1, -3, and -9 has been found on cultured endothelial cells (75), but only galectin-3 has been found to recognize *C. albicans* (41). Other PRRs that have been found to be involved in the recognition of *C. albicans* include DC-SIGN, $\alpha_M\beta_2$, FcγR, and dectin-1, but so far these receptors have not been found to be expressed on endothelial cells.

With so many different cell wall components having the potential to mediate adhesion of *C. albicans* to the endothelium, it seems that there could be a number of different mechanisms of adhesion. This may have consequences for the development of therapies aimed at blocking adhesion, because with so many molecules potentially playing a role, blocking only one could simply result in its role being taken up by other molecules. However, to investigate this further, more research is needed on the molecules involved in adhesion of *C. albicans* to the endothelial lining of blood vessels.

STATIC VERSUS FLOW ADHESION ASSAYS

The majority of the above studies that have directly explored candidal adhesion to endothelium were performed by using static in vitro assays where *C. albicans* was left in prolonged contact with cultured monolayers of endothelial cells. This is very different from the fleeting interactions *C. albicans* has with endothelial cells under the conditions of shear stress and flow that occur in blood vessels in vivo. Numerous studies with other cells and microorganisms have shown that static assays do not replicate the dynamic interactions that occur with endothelium under conditions of flow and are poor at elucidating the contributions of specific adhesion molecules (29, 47). Only a few studies have attempted to study candidal adhesion to synthetic substrata under conditions of flow. These have shown that there are significant differences in the adhesion of *Candida* to the same substrata when the assays are performed under static and flow conditions (8, 54). To date, only one study has attempted to examine the adhesion of *Candida* to endothelium under conditions of flow (29). Glee et al. found that under shear flow, *C. albicans* formed rapid, tight adhesions in less than 67 ms. This is much quicker than in static assays and is comparable to the rapid adhesion interactions that occur between leukocytes and endothelial cells. In view of this, it is difficult to fully evaluate the contributions of the mechanisms and adhesion molecules discussed above to the adhesion of *C. albicans* to endothelium in vivo, as none have been studied under conditions of flow.

TRANSMIGRATION

After adhesion of *C. albicans* to the endothelial lining of blood vessels, the second step in the migration of *C. albicans* from the circulation into the tissues is transmigration across the endothelial barrier. This step may involve some of the same molecules used for adhesion but could involve others. Transmigration is hard to research in isolation, which explains why there is little information on specific methods of *Candida*-endothelial cell transmigration. Even so, there are several proposed mechanisms for *Candida* transmigration across the endothelium (Fig. 2). The first mechanism proposes that endothelial cells endocytose adherent organisms and allow their passage through to the abluminal surface of the endothelial cell layer (Fig. 2, panel i). It is this mechanism that has gained the most interest and for which a model has evolved to explain how candidal hyphae adhere to and then induce endothelial cells to endocytose them (19, 21). In this model, *C. albicans* hyphae bind to N-cadherin and other, as yet unidentified proteins on the endothelial cell surface via the candidal protein Als3 (65). This adhesive interaction induces tyrosine phosphorylation of unidentified intracellular endothelial cell proteins (2), causing microfilament rearrangement to produce pseudopods, which initiate the endocytosis of adherent hyphal forms of *C. albicans* (22, 65). However, endothelial endocytosis of *C. albicans* is not restricted to hyphal forms, and strains that do not undergo hyphal change and cause little endothelial cell damage are endocytosed to a significant degree (40, 51, 64). Since the Als3 protein is predominantly expressed on candidal hyphae (65), this could involve other adhesin-endothelial ligand pairs. There is also evidence that suggests that adherent

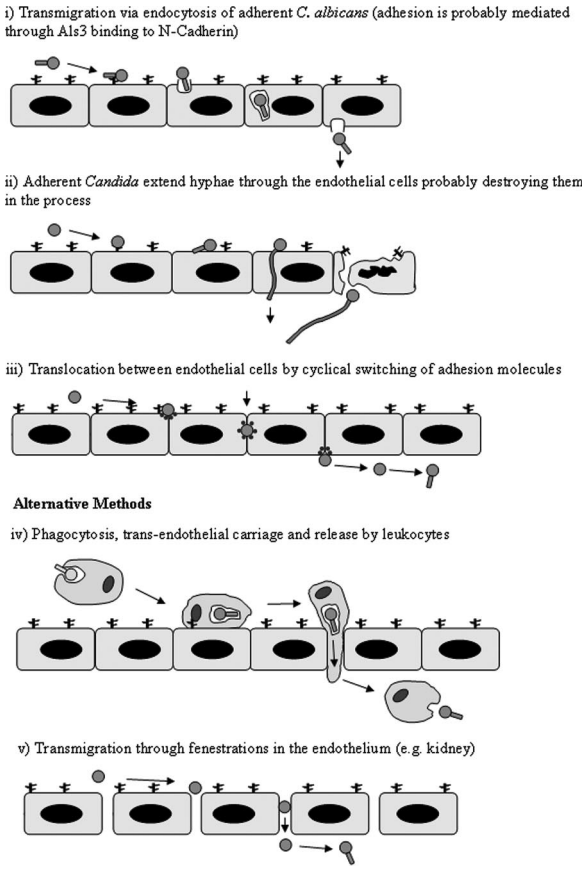

FIG. 2. Possible mechanisms for *Candida albicans* transmigration of endothelium.

yeast forms could penetrate endothelial cells, damaging them in the process, without undergoing morphogenetic change allowing them to cross the endothelial barrier (44). Another proposed mechanism of *trans*-endothelial cell migration of adherent *C. albicans* involves the extension of penetrating hyphal processes through the endothelial cells, likely destroying them in the process, much as fungal hyphae ramify through other tissues (Fig. 2, panel ii). Alternatively, a further proposal suggests that adherent *C. albicans* cells may pass between adjacent endothelial cells as a result of translocation and cyclical switching of adhesion molecules at the junction between endothelial cells, in a manner similar to that of leukocyte and tumor cell *trans*-endothelial cell migration (Fig. 2, panel iii).

Two alternative methods of transmigration across the endothelium that may not require prior adhesion of *C. albicans* to the endothelial cell surface have also been proposed. The first mechanism proposes that organisms phagocytosed by leukocytes are transported across the endothelial barrier inside the leukocytes (Fig. 2, panel iv). It is well known that leukocytes are able to cross the endothelium, between adjacent endothelial cells, by diapedesis and cyclical switching of adhesion molecules. Furthermore, there is evidence of *C. albicans* being found inside circulating leukocytes in systemic candidiasis (56). However, it is unlikely that this represents the only mechanism for candidal transmigration, since neutropenia is a major risk factor for invasive disease (35, 46). The second mechanism,

which may or may not require prior adhesion, suggests that circulating *Candida* cells simply pass through endothelial fenestrations between adjacent endothelial cells in vascular beds such as the kidney (Fig. 2, panel v).

Some of these mechanisms may operate only for the yeast, pseudohyphal, or hyphal form of *C. albicans*, some may work for all forms, and others may require morphogenetic change for transmigration to occur. As with *C. albicans* adhesion to endothelial cells, there is clearly much more research required in order to elucidate the precise mechanism by which *C. albicans* migrates across the endothelium and into the tissues. Additionally, as with leukocyte and tumor cell transmigration, the validity of these mechanisms may become apparent only when transmigration is studied in vivo or in situations where the endothelium is subject to conditions of flow (29, 47).

CONCLUSION

In summary, the interaction of *C. albicans* with the endothelial lining of blood vessels and its invasion of the tissues involve a complex series of processes that is further complicated by the role played by the morphogenetic conversion of *C. albicans*. There is still a large amount of work required to clarify these processes. Furthermore, it is important that this work be performed under conditions that replicate the fleeting contacts of *C. albicans* with the endothelium and the dynamic conditions of flow that occur in vivo. Nonetheless, understanding these mechanisms may be critical in identifying a means for preventing *Candida* invasion of the tissues and its lethal sequelae in systemic candidiasis.

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