INTERNATL MICROBIOL (1998) 1:117–122




**Jean-Marcel Senet**

Laboratoire d'Immunologie, Faculté de Pharmacie, Université d'Angers, France

# *Candida* adherence phenomena, from commensalism to pathogenicity

**Summary** Molecules present in the most external layers of *Candida* cells are essential for the adherence to host surfaces, playing a pivotal role in the pathophysiology of candidiasis. Receptors for fibrinogen, fibronectin and other components of the extracellular matrix have been described in *Candida* surfaces. Their expression may be influenced by particular host conditions, and these changes may be important in the transition from commensalism to pathogenicity. Surface proteins are also essential in the interactions of the fungal cell with the various constitutive, inducible defense host mechanisms that act during candidiasis.

**Key words** *Candida* · Candidosis/candidiasis · Adhesion/adherence · Yeast

Correspondence to:
Jean-Marcel Senet. Laboratoire d'Immunologie.
Faculté de Pharmacie.
Université d'Angers. 16 Bd Daviers.
49100 Angers. France.
Tel.: +33-241226660. Fax: +33-241486733.
E-mail: senet@univ-angers.fr

## Introduction

Almost all biological phenomena involve mechanisms of adherence. From the moment of conception to the gold medal rewarding the olympic athlete's performance, the myriad of operations carried out within the organism depend on harmonious interactions between molecules. This molecular ballet is governed by the perfect selection of complementary structures which fit together at the right time and at the right place. Basically, the interactions between molecules involve electrostatic attraction or repulsion. The strength of the electrostatic forces decreases according to the fifth power of the distance between the polarized components so that the topography of the molecules determines the possibility and, in a way, the specificity of these molecular links. At the cellular level, binding may occur at numerous sites with a weak adherence potential or may be mediated by only a few receptors with a high affinity constant for their ligand.

The nature of the ligands, the modality and the precise moment of their expression, govern the coherence of our lives. The development of organs during embryogenesis and the maintenance of tissue cohesion and of permanent remodelling require the expression of cadherins and other adhesins exactly on time; the migration of leukocytes from the bone marrow to the peripheral regions and their movement toward inflammatory areas are mediated by selectins, integrins and other adhesins belonging to the Ig superfamily. Moreover, cancer and particularly the metastatic processes also involve adherence mechanisms.

Infectious diseases are known to start with the fixation of a pathogen to a particular host target. Vaccination mechanisms have benefited largely from the possibility of raising antibodies capable of linking to these receptors to prevent the binding. In the case of candidosis, the problem is more subtle as the fungus, which can be found normally in the gastrointestinal tract and usually behaves as a commensal, can also lead to lethal systemic diseases.

Before going to the microscopic level note that candidosis is now considered, as an emergent pathogen from an epidemiological point of view. This assertion might appear to be somewhat excessive since several infections such as thrush, intertrigo, enterogastritis and others have long been known to be due to abnormal proliferation of *Candida* cells. Given the fact that *Candida* has a very important phenotypic variability and that it is usually encountered in the normal gastrointestinal flora, it becomes obvious that its so called pathogenic behaviour comes from environmental modifications, meaning here, imbalance of the host surroundings. While these modifications remain superficial, multiplication of fungi will be limited to host surfaces, held back by an effective mucosal immunity. But in the case of an important weakening of surface host defenses, fungal elements may penetrate into the intimacy of tissues, blood, and spread over in the host organism and sometimes even kill it. The considerable increase of deep seated candidosis is mostly observed in hospitals and particularly in intensive care units, cancer, organ-transplant and other departments, where most patients are subject to heavy therapeutic protocols and suffer from immunodeficiency. Antibiotherapy, corticotherapy,

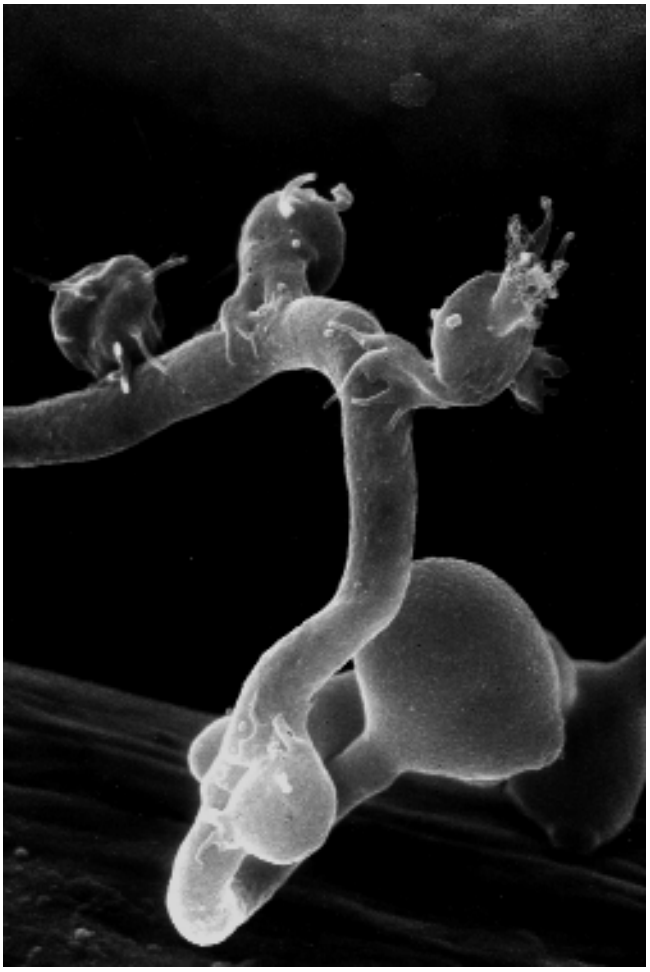

**Fig. 1** Adhesion of platelets onto the surface of *Candida albicans* germ tubes

chemotherapy and catheterism are often at the origin of these nosocomial candidosis.

The passage from a commensal to a highly pathogenic behavior, which is rather complicated, can now be analyzed at the molecular level, keeping in mind that all these steps are part of a very complex, interactive network.

## *Candida* in its "normal" habitat

As we said above, *Candida* cells usually participate in the flora of the gastrointestinal tract (GIT). About 50% of normal people have some *Candida albicans* in their stools among the many bacteria which ordinarily inhabit the GIT. The normal proliferation of these bacteria provides a barrier which regulates the multiplication of other microorganisms such as *Candida* or other potential pathogens [49]. The settlement of these microorganisms and their harmonic development depend on the amount of mucus, the peristaltism of the bowel, the presence of specific IgAs and on their capacity to adhere to epithelial cells.

The diversity of the mucus and its rapid turn-over play an important role in limiting the multiplication of *Candida* cells; their interaction with the mucus varies depending on the type of mucin and the *Candida* strain [31]. Some experiments suggest that the binding could involve oligosaccharide and lectin-like components [21, 50]. Moreover, mucinolytic enzymes may contribute to the virulence of *C. albicans* by facilitating penetration of the mucus barrier and subsequent adherence to and invasion of epithelial cells [13].

Secretory IgAs are known to protect the epithelium. Their local secretion requires the presence of gut-associated lymphoid tissues (GALT), antigen stimulation and efficient epithelial cells. Several reports suggest the role of this Ig isotype in protecting against mucosal candidosis [14, 48, 52, 71].

Binding to epithelial cells has been extensively studied by numerous authors. It is obvious that this step is necessary for the fungus prior to the penetration and colonization the underlying tissues and blood vessels. The understanding of this mechanism will help to develop new strategies for preventing such proliferation. The main approaches used involve: (i) inhibiting the fixation with identified components, (ii) analyzing the surface constituents of non-adherent *Candida* cells, and (iii) studying the role of hydrophobicity in adherence phenomena.

Most of the results demonstrate that adhesion seems related to surface hydrophobicity [23, 58]. The peptide sequence of lectin-like mannoproteins of the fungal cell-wall links to fucosyl or to N-acetyl glucosamin or galactosamin residues belonging to the surface of the epithelial cells [15, 16, 19, 20, 68]; the saccharide adhesiotope seems to be a member of the glycosphingolipid family [11, 78]. The fungal binding structures have also been described as fimbrial adhesins [77, 78], chitin [41] or integrin-like molecules [5, 27]. *Candida*-epithelium interaction provokes reciprocal signaling [4]. All these studies reveal the eclectic behaviour of *Candida* in providing adhesive components for epithelial cells.

As a commensal, *Candida* usually multiply by budding when in the blastospore form. This is an important point as *Candida* can switch its phenotype and produce long filaments which seem to be associated with the beginning of a pathogenic behaviour. This phase transition has been largely studied taking into account that the filaments are more adherent and secrete higher quantities of hydrolytic enzymes. Even a slight modification can induce the phase transition. In vivo this can be provoked by the change of the surrounding microbiota, of the pH, of the oxygen or glucose concentration, or can be the result of iatrogenic impacts [62]. Then the filamentous form, which is better equipped, can bind more strongly and even penetrate the enterocyte layer through a kind of thigmotropism [63].

## The invading *Candida*

Translocation of *C. albicans* occurs through direct penetration of enterocytes by a unique process different from classical phagocytosis. Translocation between enterocytes has not been observed. Internalization is associated with a disturbance of the plasma membrane and the brush border, but most internalized organisms are not surrounded by a plasma membrane. Passage of the *Candida* into the lamina propria appears to be associated with disruption of the basal membrane and extrusion of cell cytoplasm and *Candida* [2].

To perform all these steps, once again, *Candida* cell needs different adhesins to stick to host constituents. Receptors for many hosts proteins such as fibrinogen, fibronectin, as well as for constituents of the extracellular matrix (ECM) have been described. The route of the fungus is drawn by the interaction between the substrates and the surface fungal receptors. In addition to promote motion and settlement of the fungus, the ability to link to host constituents could provide a kind of hiding mechanism which protects it from recognition by the immune system. The invasive progression of *Candida* can be compared to metastatic cancer mechanisms involving both adhesin expression and enzyme secretion. It is also important to recall that these phenomena are dynamic and depend on the composition of the ECM which is constantly regenerated and differs from organ to organ.

*Candida* seems to express a large variety of adhesins specific for a wide array of molecules. However, it appears that the designation of the receptors is carelessly made by using the name of the substrate that they bind, which is obviously reductive. The isolation of genes coding for these adherent molecules will certainly clarify the problem.

The following substrates have been extensively studied:

(i) Fibrinogen, which plays an important role in coagulation processes, as well as in tissue repair and inflammatory reactions, binds to mannoproteins of the *Candida* cell-wall. In vivo, fibrinogen deposits which surround fungal elements in abscesses have been observed in experimentally infected mice. In vitro, purified fibrinogen was demonstrated to be principally fixed on the germ tube surface, with a dissociation constant of $5.2 \times 10^{-8}$ M. Three cell-wall mannoprotein components of respectively 60, 68 and > 200 kDa were identified. These factors were shown to bind to the D fragment and to the β chain of fibrinogen and they were also found to bind to laminin, C3d and plastic surfaces, leading to their designation as multifunctionnal adhesins of *Candida* (MFA-C) [3, 6, 7, 12, 53, 70].

(ii) Fibronectin, an adhesion promoting dimeric protein found abundantly in connective tissue and in the basement membrane, has also been shown to bind to surface glycoproteins of *Candida*. The receptor was demonstrated to have a molecular mass of 60 kDa or approximately 120 kDa according to the authors. It seems to involve an RGD adhesiotope and to belong to the integrin family. Its expression is more important on the germ tube surface and is increased in presence of hemoglobin [18, 34, 38, 39, 51, 59, 60, 64, 73].

(iii) Laminin, a large basement membrane glycoprotein [8, 43], binds to receptors closely related or similar to the MFA-C.

(iv) Complement components which participate in many biological activities, particularly following infection and inflammatory reactions. Two kinds of complement receptor (CR)-like components were evidenced on the upper surface of the *Candida* cell-wall: a CR2-like component [10, 72], and a p42-CR3-like component [1, 32]. The latter is related to the integrin family, while the first seems to be similar to the MFA-C.

Within the tissues the invading *Candida*, driven by its binding to ECM components, quickly becomes the target for professional phagocytes. Chemokines secreted by the fungus or by lysed host cells and tissues, attract the phagocytes toward the invading cells. Recognition of the fungal cell as a target may involve different mechanisms. In the case of the polymorphonuclears (PMN), which are the first to proceed and whose role is prominent in limiting the progression of *Candida*, several binding mechanisms have been reported. Intracellular adhesion molecule 1 (ICAM-1) which is an IFN-γ-dependent molecule belonging to the Ig superfamily, and selectin P and E were shown to play an important role in fixing and engulfing fungal elements. When they are coated by complement components or by immunoglobulins, PMN-CRs and FcRs can promote endocytosis. Macrophages which can operate with similar receptors possess in addition a membrane mannose receptor (MMR) that seems mainly involved in the capture of *Candida* [35]. A β-1,2-linked tetramannose residue has been demonstrated to be the *Candida* surface ligand for peritoneal macrophages [42]. These two types of cell, PMN and macrophages, are particularly important in the defense against the invading *Candida* as qualitative or quantitative deficits are often associated with systemic candidosis [17, 26, 33, 46, 66].

At this stage, it is important to note that the pivotal role taken by the phagocytic cells in binding and further destroying invading *Candida* cells is largely dependent on the help provided by lymphocytes and NK cells through the secretion of cytokines, particularly IFN-γ and TNF-α [61]. A great deal of work has been done in this field [47, 55].

Translocation can drive the fungal invader into the blood vessels. The invasion may also be due to direct contamination following catheterism [67]. Within the blood, *Candida* is rapidly coated by complement components, fibrinogen, fibronectin, and it has been demonstrated that, prior to binding to PMN, the fungal cells are quickly covered by platelets. The binding may be mediated by the platelet integrin gpIIbIIIa toward a 45 kDa mannoprotein of the *Candida* cell wall in the case of resting platelets. While activated the fixation can operate through the binding of fibrinogen and seems to be strengthened by the externalized thrombospondin. The

activated platelets were shown to release candidicidal peptides. However, the aggregates resulting from the platelet fixation can also promote the fixation of the fungus onto the endothelium of small vessels, thus leading to a kind of metastatic process [37, 44, 45, 54, 74–76]. Because of the complexity of platelets and their important role in inflammatory reactions [36], their ability to link quickly and abundantly to *Candida* cells as soon as they penetrate within the blood circulation is likely to be of great significance in the outcome of the *Candida* proliferation.

Binding to endothelial cells has also largely been studied. It can be mediated by platelets, but in the case of direct interaction, contrary to the case of epithelial cells, the linkage involves protein adhesiotopes for both sides. The fungal receptors seem to be similar to the CR-like components previously mentioned [9, 10, 22, 65] and are likely to use an RGD adhesiotope [40]. Endocytosis of *Candida* is an active mechanism, triggered by the fungal cell but carried out by endothelial cells [24, 25, 28].

Catheterism, as mentioned above, is often associated with candidemia [29]. In addition to creating a cutaneous breach which allows contamination, it constitutes a support within the blood circulation which is very convenient for the binding and proliferation of fungal cells. Moreover, once settled on a plastic surface, the germs form a biofilm which is more resistant to immune defenses as well as to antifungal therapy. Because of the numerous prosthetic devices that can be introduced into the body, the adhesion of *Candida* to plastic surfaces has been carefully investigated [30, 56, 57, 69].

## Conclusion

This short review, dedicated to underlining the role played by adhesion molecules in the behavior of *Candida*, is obviously reductive. If adherence phenomena are major events in these patho-physiological processes, they should be considered as a part of a global interplay. In vitro studies of candidal structures are little relevant to what happens in vivo. The phase transition, for example, which is well defined under in vitro conditions, seems to occur quite differently while the fungus is in the bowel. Surface components expressed on blastospores vary dramatically with their surroundings.

Moreover the jump from commensalism to pathogenicity is not so clear-cut. This provides one of the great incentives to studying host-*Candida* relationships. The so-called chronic candidosis syndrome deserves to be further investigated both from a clinical and a fundamental point of view. Until now, it has been quite impossible to find a true candidal virulence factor. Adhesin expression and enzyme secretion can obviously be considered as potential virulence factors, but the level of their synthesis and their impact in the host depend largely on the host constitution and on its capability to react against this potentially aggressive behavior.

Another interesting line of current work on *Candida* is based on the knowledge that its pathway from commensalism to systemic colonization must confront all the aspects of immunity. This include surface, mucosal, humoral and cellular aspects and all the mechanisms involved in discrimination between self and non-self which are required to cope with this particularly invasive cell. The dichotomy between Th1 and Th2 responses, establishing the advantage of the former in curing mucosal candidosis, is clearly related to the capacity of phagocytic cells to cope with the invading fungus through adherence phenomena.

## References


1. Alaei S, Larcher C, Ebenbichler C, Prodinger WM, Janatova J, Dierich MP (1993) Isolation and biochemical characterization of the iC3b receptor of *Candida albicans*. Infect Immun 61:1395–1399
2. Alexander JW, Boyce ST, Babcock GF, Gianotti L, Peck MD, Dunn DL, Pyles T, Childress CP, Ash SK (1990) The process of microbial translocation. Ann Surg 212:496–510
3. Annaix V, Bouchara J, Tronchin G, Senet J, Robert R (1990) Structures involved in the binding of human fibrinogen to *Candida albicans* germ tubes. FEMS Microbiol Immunol 64:147–154
4. Bailey A, Wadsworth E, Calderone R (1995) Adherence of *Candida albicans* to human buccal epithelial cells: Host–induced protein synthesis and signaling events. Infect Immun 63:569–572
5. Bendel CM, Stsauver J, Carlson S, Hostetter MK (1995) Epithelial adhesion in yeast species: correlation with surface expression of the integrin analog. J Infect Dis 171:1660–1663
6. Bouali A, Robert R, Tronchin G, Senet JM (1986) Binding of human fibrinogen to *Candida albicans* in vitro: preliminary study. J Med Vet Mycol 24:345–348
7. Bouali A, Robert R, Tronchin G, Senet JM (1987) Characterization of binding of human fibrinogen to the surface of germ-tubes and mycelium of *Candida albicans*. J Gen Microbiol 133:545–551
8. Bouchara J, Tronchin G, Annaix V, Robert R, Senet JM (1990) Laminin receptors on *Candida albicans* germ tubes. Infect Immun 58:48–54
9. Calderone RA, Wadsworth E (1993) Adherence molecules of *Candida albicans*. J Microbiol Meth 18:197–211
10. Calderone RA, Linehan L, Wadsworth E, Sandberg AL (1988) Identification of C3d receptors on *Candida albicans*. Infect Immun 56:252–258
11. Cameron BJ, Douglas LJ (1996) Blood group glycolipids as epithelial cell receptors for *Candida albicans*. Infect Immun 64:891–896
12. Casanova M, López-Ribot JL, Monteagudo C, Llombart-Bosch A, Sentandreu R, Martínez JP (1992) Identification of a 58-kilodalton cell surface fibrinogen-binding mannoprotein from *Candida albicans*. Infect Immun 60:4221–4229
13. Colina AR, Aumont F, Deslauriers N, Belhumeur P, Derepentigny L (1996) Evidence for degradation of gastrointestinal mucin by *Candida albicans* secretory aspartyl proteinase. Infect Immun 64:4514–4519
14. Coogan MM, Sweet SP, Challacombe SJ (1994) Immunoglobulin a (IgA), Iga1, and Iga2 antibodies to *Candida albicans* in whole and parotid saliva in human immunodeficiency virus infection and AIDS. Infect Immun 62:892–896
15. Critchley I, Douglas L (1987) Isolation and partial characterization of an adhesin from *Candida albicans*. J Gen Microbiol 133:629–636
16. Critchley IA, Douglas LJ (1987) Role of glycosides as epithelial cell receptors for *Candida albicans*. J Gen Microbiol 133:637–643
17. Davis SL, Hawkins EP, Mason EO, Smith CW, Kaplan SL (1996) Host defenses against disseminated candidiasis are impaired in intercellular adhesion molecule 1-deficient mice. J Infect Dis 174:435–439

18. Demuri GP, Hostetter MK (1996) Evidence for a beta(1) integrin fibronectin receptor in *Candida tropicalis*. J Infect Dis 174:127–132
19. Douglas LJ (1987) Adhesion of *Candida* species to epithelial surfaces. CRC Crit Rev Microbiol 15:27–43
20. Douglas LJ (1991) Adhesion of *Candida albicans* to host surfaces. In: Tümbay et al. (eds) *Candida* and Candidamycosis. New York: Plenum Press, pp 43–47
21. Edgerton M, Scannapieco FA, Reddy MS, Levine MJ (1993) Human submandibular-sublingual saliva promotes adhesion of *Candida albicans* to polymethylmethacrylate. Infect Immun 61:2644–2652
22. Edwards JE, Mayer CL, Filler SG, Wadsworth E, Calderone RA (1992) Cell extracts of *Candida albicans* block adherence of the organisms to endothelial cells. Infect Immun 60:3087–3091
23. Ener B, Douglas LJ (1992) Correlation between cell-surface hydrophobicity of *Candida albicans* and adhesion to buccal epithelial cells. FEMS Microbiol Lett 99:37–42
24. Filler SG, Ibe BO, Ibrahim AS, Ghannoum MA, Raj JU, Edwards JE (1994) Mechanisms by which *Candida albicans* induces endothelial cell prostaglandin synthesis. Infect Immun 62:1064–1069
25. Filler SG, Swerdloff JN, Hobbs C, Luckett PM (1995) Penetration and damage of endothelial cells by *Candida albicans*. Infect Immun 63:976–983
26. Fulurija A, Ashman RB, Papadimitriou JM (1996) Neutrophil depletion increases susceptibility to systemic and vaginal candidiasis in mice, and reveals differences between brain and kidney in mechanisms of host resistance. Microbiology 142:3487–3496
27. Gale C, Finkel D, Tao NJ, Meinke M, Mcclellan M, Olson J, Kendrick K, Hostetter M (1996) Cloning and expression of a gene encoding an integrin-like protein in *Candida albicans*. Proc Nat Acad Sci USA 93:357–361
28. Ghannoum M, Filler S, Ibrahim A, Fu Y, Edwards J (1992) Modulation of interactions of *Candida albicans* and endothelial cells by fluconazole and amphotericin B. Antimicrob Agent Chemother 36:2239–2244
29. Gonzalez CE, Venzon D, Lee S, Mueller BU, Pizzo PA, Walsh TJ (1996) Virus: A case-control study. Clin Infect Dis 23:515–521
30. Hawser SP, Douglas LJ (1994) Biofilm formation by *Candida* species on the surface of catheter materials in vitro. Infect Immun 62:915–921
31. Hoffman MP, Haidaris CG (1993) Analysis of *Candida albicans* adhesion to salivary mucin. Infect Immun 61:1940–1949
32. Hostetter M, Lorentz J, Preus L, Kendrick K (1989) The iC3b receptor on *Candida albicans*: subcellular localization and modulation of receptor expression by glucose. J Infect Dis 161:761–768
33. Jensen J, Warner T, Balish E (1994) The role of phagocytic cells in resistance to disseminated candidiasis in granulocytopenic mice. J Infect Dis 170:900–905
34. Kalo A, Segal E, Sahar E, Dayan D (1988) Interaction of *Candida albicans* with genital mucosal surfaces: involvement of fibronectin in adherence. J Infect Dis 157:1253–1256
35. Kitz DJ, Stahl PD, Little JR (1992) The effect of a mannose binding protein on macrophage interactions with *Candida albicans*. Cell Mol Biol 38:407–412
36. Klinger MHF (1997) Platelets and inflammation. Anat Embryol 196:1–11
37. Klotz SA, Harrison J, Misra R (1989) Aggregated platelets enhance adherence of *Candida* yeasts to endothelium. J Infect Dis 160:669–677
38. Klotz SA, Hein RC, Smith RL, Rouse JB (1994) The fibronectin adhesin of *Candida albicans*. Infect Immun 62:4679–4681
39. Klotz SA, Smith RL (1991) A fibronectin receptor on *Candida albicans* mediates adherence of the fungus to extracellular matrix. J Infect Dis 163:604–610
40. Klotz SA, Smith RL, Stewart BW (1992) Effect of an arginine-glycine-aspartic acid-containing peptide on hematogenous candidal infections in rabbits. Antimicrob Agent Chemother 36:132–136
41. Lehrer N, Segal E, Lis H, Gov I (1988) Effect of *Candida albicans* cell wall components on the adhesion of the fungus to human and murine vaginal mucosa. Mycopathologia 102:115–121
42. Li RK, Cutler JE (1993) Chemical definition of an epitope/adhesin molecule on *Candida albicans*. J Biol Chem 268:18293–18299
43. López-Ribot JL, Casanova M, Monteagudo C, Sepúlveda P, Martínez JP (1994) Evidence for the presence of a high-affinity laminin receptor–like molecule on the surface of *Candida albicans* yeast cells. Infect Immun 62:742–746
44. Mahaza C, Robert R, Miegeville M, Tronchin G, Senet JM (1991) *Candida albicans* platelet interaction: evidence for *in vivo* and *in vitro*, cell to cell attachment. In: Tümbay E et al. (eds) *Candida* and Candidamycosis. New York: Plenum Press, pp 131–135
45. Mahaza C, Robert R, Senet JM (1991) *Candida albicans*-platelet interaction: molecules involved in the adherence. In: Tümbay E et al. (eds) *Candida* and Candidamycosis. New York: Plenum Press, pp 137–141
46. Martino P, Girmenia C, Micozzi A, Raccah R, Gentile G, Venditti M, Mandelli F (1993) Fungemia in patients with leukemia. Am J Med Sc 306:225–232
47. Mencacci A, Spaccapelo R, Delsero G, Enssle KH, Cassone A, Bistoni F, Romani L (1996) CD4(+) T–helper-cell responses in mice with low-level *Candida albicans* infection. Infect Immun 64:4907–4914
48. Mendling W, Koldovsky U (1996) Immunological investigations in vaginal mycoses. Mycoses 39:177–183
49. Nair RG, Samaranayake LP (1996) The effect of oral commensal bacteria on candidal adhesion to human buccal epithelial cells in vitro. J Med Microbiol 45:179–185
50. Nikawa H, Sadamori S, Hamada T, Okuda K (1992) Factors involved in the adherence of *Candida albicans* and *Candida tropicalis* to protein-adsorbed surfaces- an in vitro study using immobilized protein. Mycopathologia 118:139–145
51. Penn C, Klotz SA (1994) Binding of plasma fibronectin to *Candida albicans* occurs through the cell binding domain. Microb Pathogen 17:387–393
52. Ponton J, Bikandi J, Arilla MC, Elosegui R, Quindos G, Fisicaro P, Conti S, Polonelli L (1996) Reactivity of *Candida albicans* germ tubes with salivary secretory IgA. J Dent Res 75:1979–1985
53. Robert R, Mahaza C, Marot-Leblond A, Tronchin G, Senet JM (1991) Binding of mouse fibrinogen to *Candida albicans in vivo*. FEMS Microbiol Lett 78:301–304
54. Robert R, Mahaza C, Miegeville M, Ponton J, Marotleblond A, Senet JM (1996) Binding of resting platelets to *Candida albicans* germ tubes. Infect Immun 64:3752–3757
55. Romani L, Cenci E, Mencacci A, Bistoni F, Puccetti P (1995) T helper cell dichotomy to *Candida albicans*: implications for pathology, therapy and vaccine design. Immunol Res 14:148–162
56. Rotrosen D, Gibson T, Edwards JJ (1983) Adherence of *Candida* species to intravenous catheters. J Infect Dis 147:594
57. Samaranayake LP, Mc Farlane TW (1980) An in-vitro study of the adherence of *Candida albicans* to acrylic surfaces. Arch Oral Biol 25:603–609
58. Samaranayake YH, Wu PC, Samaranayake LP, So M (1995) Relationship between the cell surface hydrophobicity and adherence of *Candida krusei* and *Candida albicans* to epithelial and denture acrylic surfaces. APMIS 103:707–713
59. Santoni G, Birarelli P, Hong LJ, Gamero A, Djeu JY, Piccoli M (1995) An alpha 5 beta 1 -like integrin receptor mediates the binding of less pathogenic *Candida* species to fibronectin. J Med Microbiol 43:360–367
60. Santoni G, Gismondi A, Liu JH, Punturieri A, Santoni A, Frati L, Piccoli M, Djeu JY (1994) *Candida albicans* expresses a fibronectin receptor antigenically related to alpha 5 beta 1 integrin. Microbiology 140:2971–2979
61. Senet JM (1996) Physiopathologie des candidoses. Rev Med Interne 17:343s–345s
62. Senet JM (1997) Risk factors and physiopathology of candididasis. Rev Iberoam Micol 14:6–13

63. Sherwood J, Gow NAR, Gooday GW, Gregory DW, Marshall D (1992) Contact sensing in *Candida albicans* - a possible aid to epithelial penetration. J Med Vet Mycol 30:461–469
64. Skerl K, Calderone R, Segal E, Streevalsan T, Scheld W (1983) In vitro binding of *Candida albicans* yeast cells to human fibronectin. Can J Microbiol 30:221–227
65. Spotl L, Most J, Dierich MP (1994) $Ca^{2+}$ ions stabilize the binding of complement factor Ic3B to the pseudohyphal form of *Candida albicans*. Infect Immun 62:1125–1127
66. Swerdloff JN, Filler SG, Edwards JE (1993) Severe candidal infections in neutropenic patients. Clin Infect Dis 17:S457–S467
67. Taylor GD, Buchananchell M, Kirkland T, Mckenzie M, Wiens R (1994) Trends and sources of nosocomial fungaemia. Mycoses 37:187–190
68. Tosh, FD, Douglas LJ (1992) Characterization of a fucoside-binding adhesin of *Candida albicans*. Infect Immun 60:4734–4739
69. Tronchin G, Bouchara J, Robert R, Senet JM (1988) Adherence of *Candida albicans* germ tubes to plastic: ultrastructural and molecular studies of fibrilar adhesins. Infect Immun 56:1987–1993
70. Tronchin G, Robert R, Bouali A, Senet JM (1987) Immunocytochemical localization of in vitro binding of human fibrinogen to *Candida albicans* germ tube and mycelium. Ann Inst Pasteur /Microbiol 138:177–187
71. Vudhichamnong K, Walker DM, Ryley HC (1982) The effect of secretory immunoglobulin A on the in vitro adherence of the yeast *Candida albicans* to human oral epithelial cells. Arch Oral Biol 27:617–621
72. Wadsworth E, Prasad SC, Calderone RA (1993) Analysis of mannoproteins from blastoconidia and hyphae of *Candida albicans* with a common epitope recognized by anti-complement receptor type-2 antibodies. Infect Immun 61:4675–4681
73. Yan SH, Negre E, Cashel JA, Guo NH, Lyman CA, Walsh TJ, Roberts DD (1996) Specific induction of fibronectin binding activity by hemoglobin in *Candida albicans* grown in defined media. Infect Immun 64:2930–2935
74. Yeaman MR, Ibrahim AS, Edwards JE, Bayer AS, Ghannoum MA (1993) Thrombin-induced rabbit platelet microbicidal protein is fungicidal in vitro. Antimicrob Agent Chemother 37:546–553
75. Yeaman MR, Soldan SS, Ghannoum MA, Edwards JE, Filler SG, Bayer AS (1996) Resistance to platelet microbicidal protein results in increased severity of experimental *Candida albicans* endocarditis. Infect Immun 64:1379–1384
76. Yeaman MR, Sullam PM, Dazin PF, Ghannoum MA, Edwards JE, Bayer AS (1994) Fluconazole and platelet microbicidal protein inhibit *Candida* adherence to platelets in vitro. Antimicrob Agent Chemother 38:1460–1465
77. Yu L, Lee KK, Paranchych W, Hodges RS, Irvin RT (1996) Use of synthetic peptides to confirm that the *Pseudomonas aeruginosa* PAK pilus adhesin and the *Candida albicans* fimbrial adhesin possess a homologous receptor-binding domain. Mol Microbiol 19:1107–1116
78. Yu L, Lee KK, Sheth HB, Lanebell P, Srivastava G, Hindsgaul O, Paranchych W, Hodges RS, Irvin RT (1994) Fimbria-mediated adherence of *Candida albicans* to glycosphingolipid receptors on human buccal epithelial cells. Infect Immun 62:2843–2848