

## Complement in *Candida albicans* infections

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## 1. ABSTRACT

Being normally a frequent commensal organism of the oro-gastrointestinal tract as well as the vulvovaginal cavity in immunocompetent individuals, *Candida albicans* also represents a major cause of opportunistic infections in locally or systemically immunocompromised hosts. Subsequent symptoms vary and range from superficial thrush to life-threatening systemic infections. The complement system is one of the first defenders of the body against this danger and initiates a fast and efficient antifungal reaction. However, *Candida* is not an easy prey and counteracts with different complement evasion strategies to undermine this innate immune system. In the present article we summarize the different rounds in the fight between *C. albicans* and the complement system, and give a short outlook on putative complement-based therapeutic approaches.

## 2. INTRODUCTION

Despite all medical progress fungal infections are still a burning problem; and medical progress such as organ transplantation, leukemia treatment and improved antiretroviral therapy against human immunodeficiency virus (HIV) even contributes to the growing number of immunocompromised patients susceptible for fungal pathogens (1). *Candida albicans*, the most frequently isolated yeast, is a ubiquitous saprophyte of mucous membranes of gastrointestinal tract and of vulvovaginal and oral cavities. In immunosuppressed patients endogenous infections emanating from these colonization sites can occur with cutaneous infections, oroesophageal candidiasis, *Candida* vaginitis and septicemia (1, 2, 3).

The dissemination of *Candida* leads to a broad spectrum of interactions between the yeast and the immune

system of the host (4, 5). Although the immunological situation varies significantly between different organs, complement is a universal antimicrobial defense system which fights everywhere in the body. After activation the powerful complement weapon exerts a variety of antimicrobial effects and thus represents a central host factor to limit fungal proliferation and pathogenesis. To counteract this limitation and to avoid complement-induced elimination *Candida* like many other pathogens has developed evasion strategies (6). The present article summarizes the multifaceted spectrum of interactions between complement and *Candida*.

### 3. THE COMPLEMENT SYSTEM

Complement represents a cascade of sequential activation and polymerization steps, mainly built up by nine soluble protein factors. Essential cofactors as well as an army of soluble and membrane-bound regulator proteins expand the number of participating players. Furthermore various receptors complete the arsenal of complement proteins to a final number of approximately 30 molecules (7).

#### 3.1. Triggering signals by and functions against *Candida* infection

The pathogenesis of an infection by *Candida* either disseminated or locally in the tissue, provides three conditions which lead to an activation of the complement cascade (6):

- appearance of foreign surface patterns, e.g. carbohydrates (PAMP = pathogen-associated molecular pattern)
- antigen/antibody complexes after seroconversion
- presence of cell debris due to the inflammation process

These three infection-induced disturbances in the homeostasis of the body alert the sensor molecules of the complement system which are equipped with interaction domains for PAMPs, immune complexes and/or cell debris.

In general, the output of the *Candida*-induced complement activation can comprise a variety of antimicrobial reactions (6):

- direct lysis of the pathogen by formation of a lytic pore in the pathogen's surface
- opsonization of the pathogen to designate it for phagocytes and phagocytic killing
- chemotactic attraction of immune cells to the site of infection
- cell activation with stimulation of signaling pathways
- stimulation of humoral immune response and of T-cell response, thus forming a network between innate and adaptive immunity
- modulation of cytokine expression

- clearance of immune complexes and cell debris

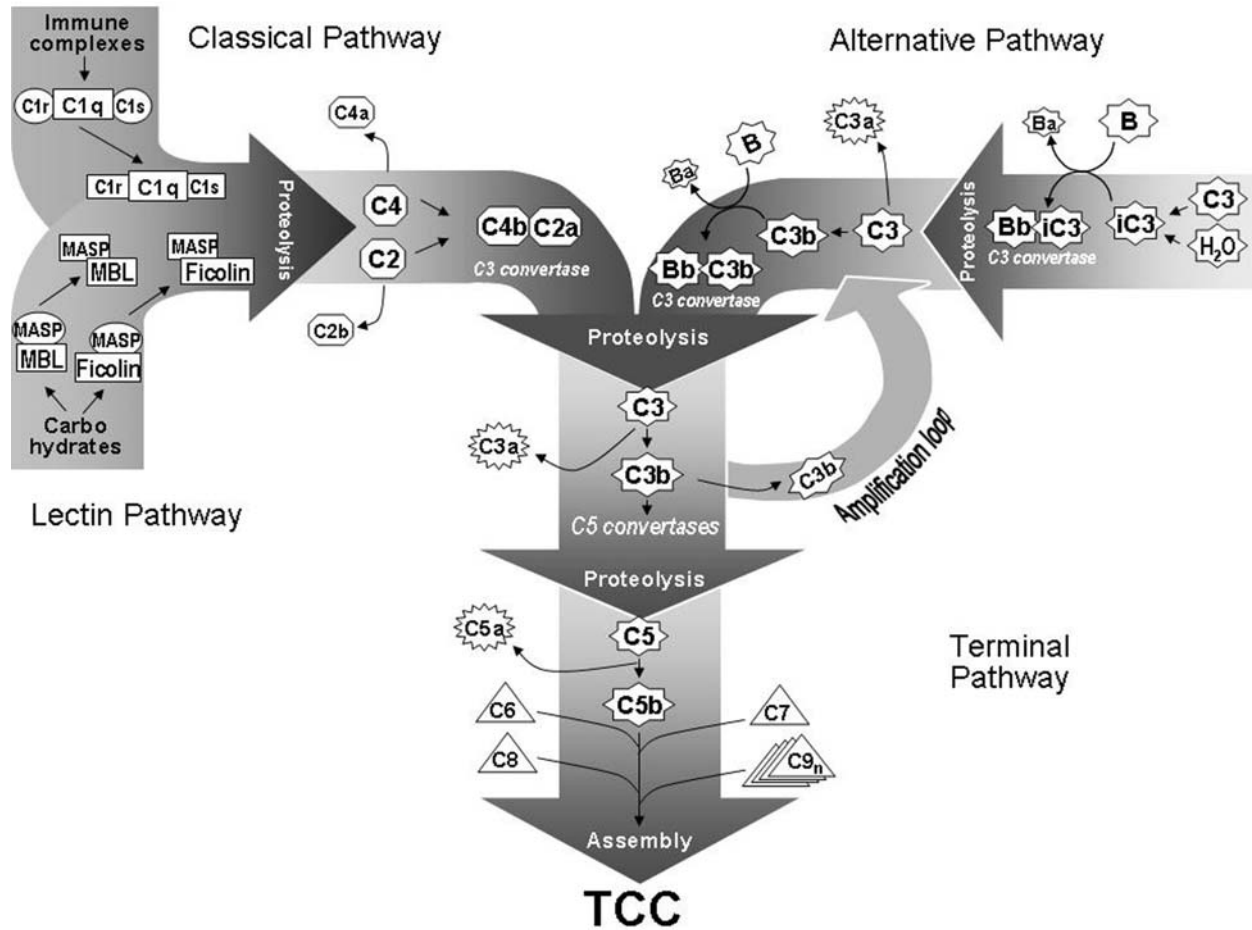
#### 3.2. Activation steps and terminal part of the complement cascade

Three different pathways of activation are distinguished, initiated by either target-bound antibodies (the classical pathway), by microbial repetitive polysaccharide structures (the lectin pathway), or by recognition of other "foreign" surface structures (the alternative pathway) (Figure 1). The alternative pathway also amplifies the activation triggered by the other two ways. All three merge in the pivotal cleavage of complement factors C3 and subsequently C5 by highly specific proteolytic enzyme complexes, so-called convertases. In the common terminal pathway downstream of C5 further complement components are activated in a non-proteolytic manner and assembled into the membrane attack complex (MAC, TCC) (8).

In the classical pathway complement factor C1q interacts with the constant portion (Fc) of the immunoglobulins IgG or IgM if and only if they are bound within antigen-antibody complexes. Furthermore some few examples show the possibility of antibody-independent linkage of C1q to pathogen proteins and subsequent initiation of the classical pathway. Both steps activate the C1q-associated proteases C1r and C1s which cleave the complement factors C2 and C4 and thus enable the accumulation of the so-called C3-convertase C4bC2a from the larger fragments of both proteins. Mannan-binding lectin (MBL) or the structurally related ficolins are the starter molecules of the lectin pathway when they interact with a range of carbohydrate structures on the surface of the pathogen. The activation and action of MBL-associated proteases (MASPs) results in the formation of the same convertase C4bC2a (Figure 1). In the alternative pathway the recognition of foreign surface structures induces an amplification loop of spontaneously formed C3(H<sub>2</sub>O) or of C3b generated either by inflammatory proteases or by activation via the other two pathways. The final product of the alternative pathway is the C3-convertase C3bBb, formed by proteolytic cleavage of factor B after association with C3b (8).

Both C3-convertases C4bC2a and C3bBb are enzyme complexes which catalyze the cleavage of complement factor C3 that represents the central multifunctional element of the complement cascade. The resulting small peptide C3a is a versatile anaphylatoxin. As a potent proinflammatory mediator it recruits receptor-bearing cells and triggers their chemotactic migration. Another central inflammatory potency of C3a lies in its capacity to stimulate the release of cytokines and histamine. It is spasmogenic, stimulates the release of prostaglandin E2 (PGE2) from macrophages, and induces degranulation of mast cells (9).

The larger fragment of C3 which is generated by the proteolysis, C3b, changes its conformation and binds to nearby nucleophilic sites, e.g. OH-groups of any surrounding molecule. The complex of the respective C3 convertase and the additional C3b molecule forms the C5 convertase and mediates the scission of C5, a step which represents a



**Figure 1.** The course of the complement cascade with the participating proteins. Three activation pathways (classical, lectin, alternative) initiate the cascade after contact with different stimuli. Proteolytic steps executed by so-called C3 convertases flow together in the central step of complement factor C3 cleavage. Further proteolysis as well as consecutive assembly steps result in the generation of the terminal complement complex TCC. The cleavage products C3a and C5a act as anaphylatoxins with potent biological activity. For further details see text.

prerequisite for the following activation of the terminal pathway. The smaller fragment C5a is an anaphylatoxin with biological activity similar to C3a but higher potency (10). The larger s product C5b starts the final aggregation and polymerization steps of the complement cascade: the terminal complement components C6, C7, C8 and C9 are sequentially, but non-enzymatically, activated and form the terminal complement complex (TCC). On a cellular target membrane the TCC can be generated as membrane attack complex (MAC) which efficiently lyses cells by insertion of C9 cylinders into the lipid layer. Alternatively, TCC forms in extracellular fluids as non-lytic SC5b-9 (11) (Figure 1).

### 3.3. Regulatory intervention in the complement cascade

The multiple biological functions of activated complement demand a strict control to avoid an excessive inflammatory reaction and to prevent tissue damage. For these purposes a variety of membrane bound and soluble regulator proteins act at different steps of the cascade.

The classical and the lectin pathway are

controlled by C1-INH which inactivates the associated proteases and therefore inhibits the generation of the C3-convertase C4bC2a (12). A further control of these two ways is assured by the regulatory C4 binding protein (C4bp). It acts as a cofactor of the serum protease factor I (fI) that cleaves and thus inactivates both C4b and C3b; in addition C4bp accelerates the decay of C4bC2a. The alternative pathway with the self-amplification of C3b is controlled by factor I together with factor H (fH), factor H-like protein 1 (FHL-1), complement receptor 1 (CR1, CD35) and membrane cofactor protein (MCP, CD46) as essential cofactors (8).

All convertases for cleavage of C3 and C5 are destabilized by fH, CR1 and decay accelerating factor (DAF, CD55) with the consequence of a rapid disassembly of the complex. Furthermore, factor I and its cofactors fH, FHL-1, CR1 and MCP prevent the generation of the C5 convertases by degrading C3b. The anaphylatoxins C3a and C5a are also subject of control mechanisms; the carboxypeptidase N is able to remove the carboxyterminal arginine from both peptides and thus inactivate them (8).

The terminal steps of the complement cascade are monitored by S-protein and clusterin that can bind to nascent C5b-7 and prevent its membrane insertion. The final step of MAC assembly is controlled by protectin (CD59) which interferes with the polymerization of C9 on the membrane (8).

### 3.4. Complement receptors (CR)

Specific cellular receptors “translate” the presence of activated complement proteins and of fragments derived thereof into biological functions such as changes in cell functions, support of adaptive immunity and the enhancement of innate immune responses to eliminate foreign or damaged material (microbes, apoptotic cells, immune complexes). The complement receptors CR1, CR2, CR3 and CR4 as well as CR1g (complement receptor of the immunoglobulin superfamily) all recognize C3 fragments that are covalently bound to foreign/abnormal surface structures. Consequences of the ligand-receptor interaction are uptake of such opsonized particles and the subsequent activation of appropriate intracellular signalling pathways.

The receptor CR1 (CD35) is a bifunctional molecule with receptor sites for C3b and C4b as well as regulator activity for the complement cascade. A broad spectrum of peripheral blood cells expresses CR1 on the surface, predominantly erythrocytes, where CR1 mediates the transport of C3b/C4b-coated antigen/antibody complexes to liver and spleen for subsequent removal by phagocytic cells. With its presence on phagocytes CR1 arranges the ingestion of opsonized pathogens or cell debris. CR1 on B-cells plays a role in B-cell proliferation and differentiation (13).

The complement receptor CR2 is detected predominantly on B-cells and follicular dendritic cells (FDC) where it interacts with C3d, C3dg, and iC3b as putative ligands. The binding of CR2 on B-cells to C3d-opsonized antigens significantly supports B-cell activation with subsequent antibody maturation and induction of B-cell memory, thus bridging the innate with the adaptive immunity (14, 15).

CR3 (CD11b/CD18, alpha-M-beta-2, Mac-1) is a member of the beta-2 integrin family and is composed of the alpha-chain CD11b and the beta-chain CD18 (16). The receptor is found on mononuclear phagocytes, neutrophils, mast cells and NK-cells, FDC and T-cell subsets. Besides the binding to the fragment iC3b, CR3 can interact with numerous ligands, including ICAM-1 and -2 (intercellular adhesion molecule), proteins of the clotting system, and several molecules of microbial origin. It is the main receptor for phagocytosis of iC3b-opsonized pathogens, but also contributes considerably to leukocyte adherence and migration. CR4 (CD11c/CD18) belongs to the same beta-2 integrin subfamily as CR3 and harbors similar cell distribution, ligand specificities and functions (8).

A similar role in clearance of opsonized pathogens can be attributed to the recently discovered receptor CR1g (VSIG4: V-set and Ig domain-containing 4). Expressed on tissue macrophages it recognizes C3b, C3c

and iC3b (17). As a potent negative regulator of T-cell response CR1g bridges innate with adaptive immunity. Since ligand binding triggers the internalization of CR1g an activation of the complement might remove the macrophage-induced T-cell inhibition and thus promote inflammation (18). Similar to CR1, CR1g combines the receptor function with a function as a complement regulator. As a potent and specific inhibitor of the alternative pathway CR1g interferes with the binding of C5 to the C3-convertase (19, 20).

The biological functions of the anaphylatoxins C3a and C5a are mediated by binding to the surface receptors C3aR, C5aR (CD88) and C5L2. C3aR and C5aR are found on cells of myeloid origin as well as on epithelial, endothelial and parenchymal cells, B- and T-lymphocytes. C5L2 is expressed on immature DCs, neutrophils and adipocytes. After binding of C5a its receptor C5aR induces the corresponding proinflammatory activities such as chemotactic migration, secretion of cytokines, enhancement of cell adhesion and stimulation of oxidative burst (21). In contrast, the second C5a receptor, C5L2, couples only weakly to the signalling G-proteins and might thus serve as a non-signalling decoy receptor in order to limit the C5a-induced inflammation (22). The receptor C3aR binds to the less potent anaphylatoxin C3a and mediates its pro-inflammatory actions which overlap with those of C5a.

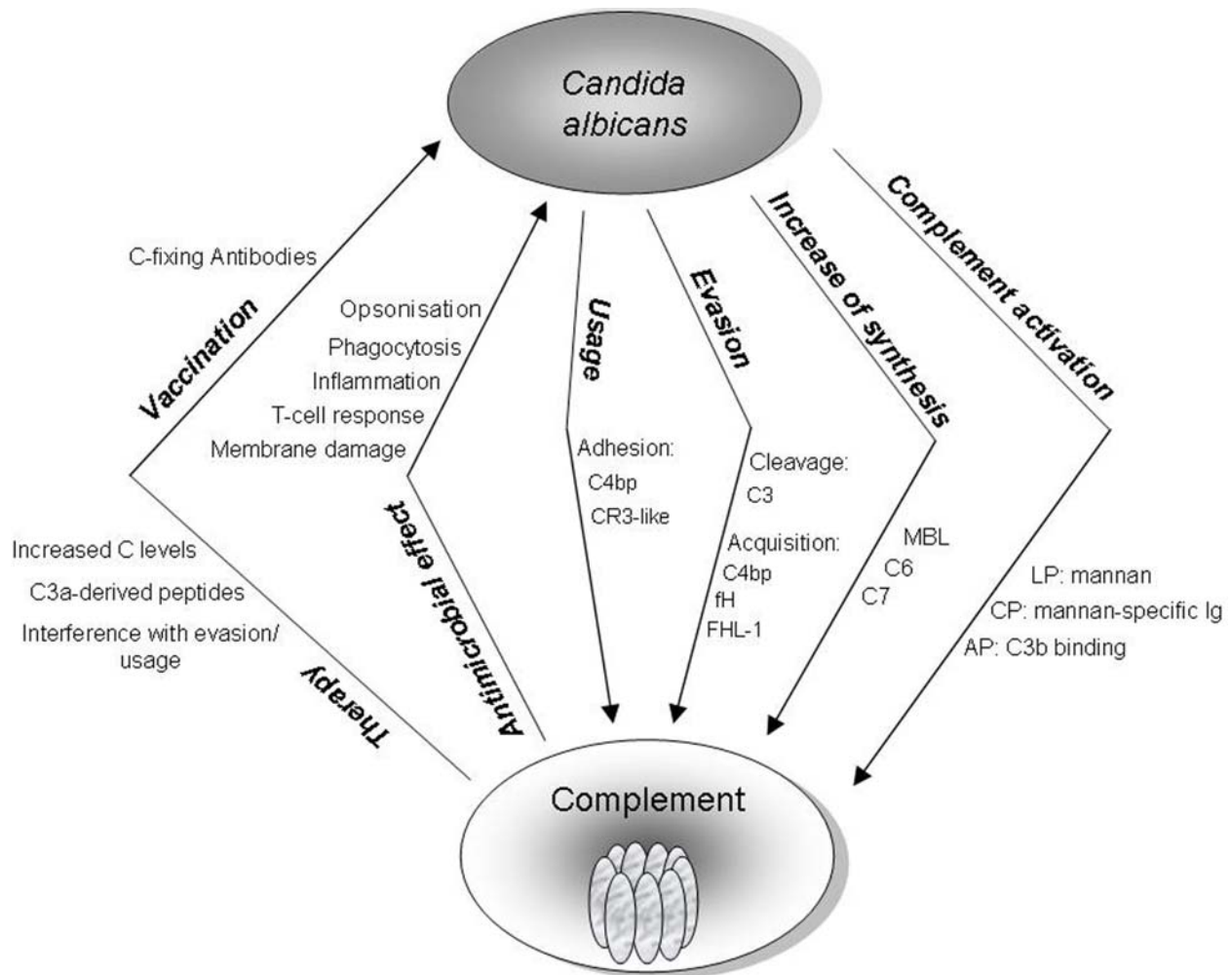
A variety of receptors are described for complement factor C1q, such as C1qRp, gC1qR, cC1qR and the newly identified alpha-2-beta-1 integrin. The binding of the ligand to its receptor(s) can enhance phagocytosis or oxidative burst metabolism (23).

## 4. THE FIGHT “HOST AGAINST FUNGUS”, ROUND 1: COMPLEMENT AGAINST *CANDIDA*

### 4.1. The significance of complement in candidiasis

Complement activation and the associated antimicrobial effects are central components in the immune fight against *Candida albicans* infections. This role is reflected by the fact that the host reacts with a fast and efficient upregulation of complement levels to the contact with the yeast, either by stimulation of synthesis or by increased secretion. Cervicovaginal concentrations of MBL are significantly higher in patients with vulvovaginal candidiasis than in non-infected individuals (24). Stimulation of polymorphonuclear leukocytes (PMNs) with opsonized *C. albicans* induces a sustained release of C6 and C7 into the cell culture supernatant within a few minutes after addition of the trigger (25) (Figure 2). Additional evidence for the role of complement in antifungal host resistance arises from the correlation between complement levels and susceptibility to *Candida* infections. A genetic polymorphism in the MBL gene which results in reduced assembly and stability of the protein and consequently in lower MBL levels in the vagina predisposes to recurrent vulvovaginal candidiasis (26, 27).

The role of complement in candidiasis has also been demonstrated *in vivo* by animal models. Complement depletion with cobra venom factor (CVF) results in a higher mortality rate in guinea pigs with *Candida* infection compared



**Figure 2.** Mutual interaction between *Candida albicans* and the complement system. Infection by *C. albicans* induces complement activation via the lectin (LP), classical (CP) and alternative (AP) pathway, with mannan, mannan-specific immunoglobulin (Ig) and binding of C3b as the corresponding inducer. *C. albicans* stimulates the synthesis of complement factors MBL, C6 and C7 in the body. Evasion mechanisms such as cleavage of C3 and acquisition of C4bp, fH and FHL-1 protect the fungus from efficient clearance by the complement system. *Candida* even uses acquired C4bp as well as own CR3-like molecules to adhere to host tissue. On the other hand, complement applies various mechanisms for antifungal attack: opsonization and assistance of phagocytosis, inflammatory processes, support of T-cell response and damage of microbial membranes. Complement-based therapeutic approaches might aim to increase complement concentrations, to use C3a-derived peptides with its antifungal effects, or to interfere with fungal evasion and usage of complement molecules. An anti-*Candida* vaccination must guarantee the generation of complement-fixing antibodies, a prerequisite for protection. For further details see text.

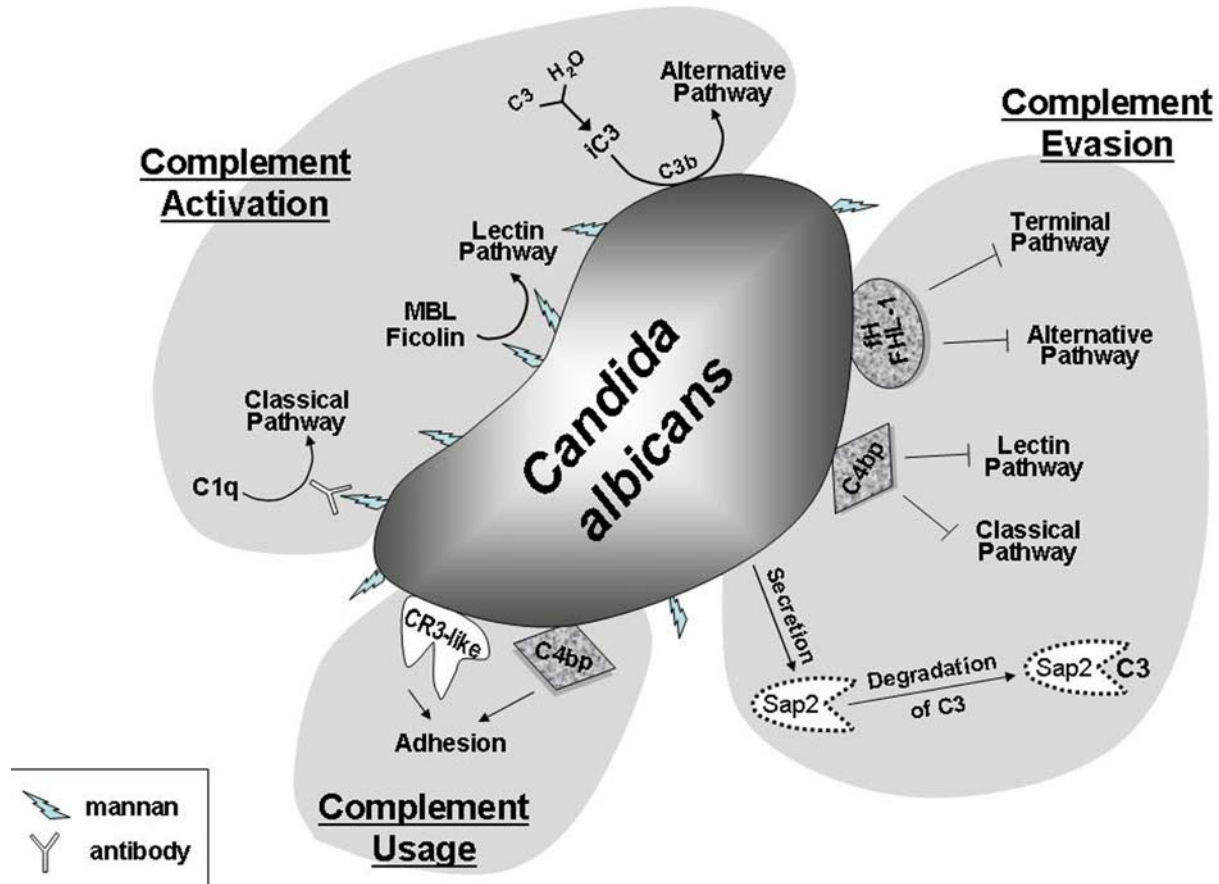
to control animals (28). In contrast to complement-competent mice, C5-deficient animals or those treated with CVF fail to develop significant neutrophilic inflammatory response after intradermal infection with *C. albicans* and readily permit fungal proliferation into the subcutaneous fat tissue (29).

Further emphasis of the significance of complement for the antifungal defense comes from patients with deficiencies in the control proteins factor I and/or factor H that are associated with increased consumption of C3. When *C. albicans* yeast cells are incubated with serum taken from such an individual opsonization and killing by peripheral leukocytes are reduced (30).

#### 4.2. The different activation pathways of the complement cascade in candidiasis

*Candida albicans* is a strong activator of all three pathways of the complement system as shown by numerous studies in vitro as well as in vivo (31). Animal models show complement deposition in the lesions of mucocutaneous candidiasis and in *Candida* mastitis (32, 33, 34).

The classical pathway is triggered by the presence of mannan-specific antibodies (35, 36). Mannan, a major cell wall component of all *Candida* species, consists of O-linked oligomannosides and N-linked mannose polysaccharides and represents the major antigenic determinant of the fungal



**Figure 3.** Mechanisms of *Candida*-induced complement activation with consecutive evasion strategies and fungal usage of complement molecule for the microbe's purposes. The different complement activation pathways after contact with the fungal surface are shown. Complement evasion is based on acquirement of C4b as well as of fH and FHL-1 and subsequent inhibition of the lectin, classical, alternative and terminal pathway. The second evasion strategy consists in the secretion of the protease Sap2 which degrades the protein C3. The complement usage comprises the support of fungal adhesion to tissue structures by C4bp acquired from the host as well as a CR3-like molecule on *Candida* mimicking the human CR3 and interacting with its corresponding counter-receptors.

surface. Naturally occurring antibodies reactive with *Candida* mannan epitopes are present in the serum of most normal individuals, but differ between individuals regarding titers, binding specificities and protective capacity. There is a clear-cut correlation between the protective potential of the antibodies and their capacity to bind C3b to the yeast cell: protective antibodies induce the deposition of C3b more efficiently to the fungal surface than non-protective antibodies (37, 38, 39). The antimannan immunoglobulin-induced accumulation of C3b via the classical pathway is an extremely rapid process occurring within 1 min after contact with the yeast cell. Serum derived from individuals with high titers of naturally occurring antimannan antibodies leads to a faster deposition of C3b on the fungal wall than serum from persons with low titers (40). The C3b molecules bound via classical pathway are uniformly distributed over the entire yeast cell surface (35) (Figure 2, 3).

The pattern recognition molecule MBL of the lectin pathway binds strongly to mannoproteins on the *Candida* surface, both of the yeast and of the pseudohyphal phenotype.

Many of the mannose residues found in *Candida* mannan present hydroxyl groups in the 3-OH and 4-OH position that is needed for MBL recognition (41). The MBL-mediated activation of the lectin pathway results in deposition of C3 fragments on the fungal surface (42) (Figure 2, 3).

The deposition of C3 via the alternative complement pathway exhibits characteristics which differ from that of the classical pathway (31, 36). Binding of the initial C3b molecules by alternative pathway requires with 12 min a much longer incubation time than by the classical pathway. Furthermore, C3 molecules deposited by the alternative pathway are not distributed homogeneously but are found at a few discrete sites of the yeast cell surface (35, 36) (Figure 2, 3).

It is difficult to determine which pathway is the predominant one in antifungal defense, and this decision might depend considerably on the body compartments. In vulvovaginal candidiasis the alternative pathway is supposed to dominate the complement activation, since C1q was

undetectable on the *Candida* hyphae (43). Furthermore MBL from the lectin pathway seems to be unable to bind *Candida* in the low pH condition of the vagina (43). In blood the classical pathway might play a central role, since the rate of initial C3 binding to yeast cells correlated well with the titer of antimannan antibodies circulating in the sera of different individuals (44). However, in the guinea pig model of disseminated candidiasis no difference in mortality was found between C4-deficient and control animals (28), indicating a minor role of the classical pathway at least in this model. Many studies underline the central significance of the alternative pathway in the fight against *Candida*. Strong complement activation by *C. albicans* occurred in C2-deficient as well as in C4-deficient human serum and thus in the absence of classical and lectin pathway (45).

### 4.3 Antimicrobial effects of complement in *C. albicans* infections

The antifungal potency of activated complement is based on a broad spectrum of efficient mechanisms. Direct lysis of the yeast cell via integration of the membrane attack complex is rather unlikely due to the thickness and complexity of the cell wall (45). However, the triggering of all three pathways results in the deposition of complement fragments on the yeast surface and in the release of activation products with biological functionality.

The surface deposition of complement promotes phagocytosis and phagocytic killing of *C. albicans* yeast cells by macrophages and neutrophils (46, 40, 47). The phagocytosis by polymorphonuclear leukocytes (PMNs) as well as the intracellular killing were largely reduced in serum wherein complement was inactivated by heat (48). Serum samples from a patient with factor I deficiency and thus largely consumed C3 allowed only decreased opsonization and killing of the yeast by peripheral leukocytes (30).

The adherence of effector cells to the yeast is the first step for these processes of phagocytosis and killing (49). Complement receptors, particularly CR3 (CD11b/CD18), are of central significance for this cell-mediated antifungal defense. Patients with defects in or a lack of CD18-integrins are highly susceptible for candidal skin infections and esophagitis (50). The yeast is recognized by complement receptor CR3 either in its non-opsonized form via beta-glucan and mannan polysaccharides or after opsonization via bound C3b/iC3b. The interaction sites of CR3 with the yeast are mapped to the I domain and the lectin-like domain of CD11b; CD18 modulates this process (51, 52). Phagocytosis of *C. albicans* by PMNs and subsequent oxidative burst can be inhibited by blockade of CR3 via monoclonal antibodies (53). CR3 is also the principal adhesion receptor for *C. albicans* on neutrophils, macrophages and lymphocytes (52). The interaction between CR3 on lymphocytes and the yeast is the prerequisite for the resultant antifungal effects such as inhibition of *Candida* hyphal growth and induction of cytokines that modulate the antifungal activity of other immune cells (54). These immune reactions via contact of lymphocytic CR3 to *Candida* are probably the principal defense mechanisms on mucosal and epidermal surfaces.

CR3 on dendritic cells (DC) mediates the entry of opsonized and non-opsonized *C. albicans* yeasts and hyphae,

thus modulating both Th1 and Th2 responses (55). Interestingly this interaction of DC with the fungus leads to suppression of the antifungal immune response (49).

Besides the role of CR3, the presence of terminal complement components and thus the formation of the membrane attack complex augment phagocytosis by an as yet unknown mechanism (56).

The pattern recognition molecule MBL of the lectin pathway does not only trigger complement activation, but also harbors some additional functions. MBL was found to inhibit the growth of *C. albicans* independently of complement activation, although inhibition was more pronounced in the presence of activated complement (42). Furthermore, MBL enhances the release of the cytokine tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) from monocytes after exposure to *Candida albicans*, thus promoting the antifungal inflammatory response (57). Also the anaphylatoxin C3a, a cleavage product of factor C3 possesses strong antimicrobial effects against *Candida*. C3a and C3-derived peptides comprising different helical regions of the C3a molecule bind to the cell surface of *Candida* and induce membrane perturbations and fungal killing by an as yet unknown mechanism (58). The antifungal effects of the complement system are summarized in Figure 2.

Not only the direct antimicrobial functions described as yet make complement a fundamental weapon against *Candida*, but also the complement-induced modulation and control of other arms of the immune system. Due to a mutation in C5 the mouse strain A/J is exquisitely sensitive to infection with *C. albicans* (59). This C5 deficiency is associated with an inability to mobilize granulocytes and a high fungal load after infection with *Candida*, but also with highly elevated levels of various circulating cytokines and chemokines. This exaggerated cytokine induction in response to *Candida* can be recapitulated to congenic mice by transfer of the defective C5 allele, indicating that the C5-derived peptide C5a plays a role not only in the initiation of inflammation but also in the subsequent control of this inflammatory response (59, 60). By downmodulating the antimicrobial inflammation C5 may help to reduce detrimental effects on the host, possibly through a negative feedback mechanism (61).

## 5. THE FIGHT “HOST AGAINST FUNGUS”, ROUND 2: *CANDIDA* AGAINST COMPLEMENT

In the course of the host-pathogen altercation *Candida albicans* has developed several strategies to compete with the complement system or to even use parts of the host defense for its own purposes (6, 62) (Figure 2, 3).

A mechanism which is also used by other pathogens is the secretion of extracellular proteases that degrade complement proteins. *C. albicans* is known to produce a number of secreted aspartic proteases (Sap) which represent important virulence factors to overcome host barriers against fungal infections (63). At least one of these proteases, Sap2, has been shown to cleave complement factor C3, resulting in decreased opsonization of the pathogen and

diminished phagocytosis by PMNs (64, 65). Interestingly Sap2 was also demonstrated *in vivo* to be one of the predominantly expressed proteinase genes in patients with vulvovaginal candidiasis, a disease where complement is known to play an important role in antifungal defense (66) (Figure 2, 3).

A second evasion mechanism is the acquisition of host-derived inhibitory proteins to prevent complement activation on the fungal surface. As described above, the dangerous weapon of complement is tightly controlled by a broad range of membrane-bound and soluble regulatory proteins (8). Originally designed for the protection of tissue cells from harmful effects, *C. albicans* has learnt to acquire three of the soluble complement regulators from the host and to capture them to its surface: the factor H, its relative factor H-like protein 1 (FHL-1) and C4bp (67). These three regulators are closely related molecules as they are composed of variable numbers of short consensus repeat (SCR) domains (68). They also partly share their mode of action by accelerating the decay of the C3- and C5-convertases and by serving as cofactors for the serine protease factor I (fi) which cleaves and inactivates C3b and C4b (8). By the acquisition of these broad-acting regulators on the fungal surface *Candida* can paralyze all three pathways of complement activation at central steps of the cascade.

Factor H and FHL-1 share a *C. albicans* binding domain in the N-terminal SCRs 6 and 7; an additional one of factor H is located in the C-terminal SCRs 19 and 20. On the side of *C. albicans* one of the corresponding receptors for the regulator proteins may have been found recently (69). As the human CR3 is a receptor for factor H (70), it is tempting to speculate that a related CR3-like protein expressed by *C. albicans* (see below) might represent a binding site for fH and FHL-1 (71). The attachment of the regulators equips *Candida* with a potent cofactor activity for fi-mediated cleavage of C3b, resulting in decay of all surface-bound C3- and C5-convertases and in inhibition of binding of further C3b molecules to the yeast (70, 71).

Both yeast and hyphal forms of *C. albicans* are able to capture C4bp from serum (72, 73). Attachment to the fungal surface is mediated by the SCRs 1 and 2 on the alpha-chain of C4bp. On hyphae, a prominent binding site was identified at the tip and is therefore considered to be important for tissue penetration and pathogenesis. The receptor molecule on *Candida* for C4bp might be the same as for FHL-1, since both proteins compete for the binding to the yeast (67, 73). *Candida*-bound C4bp maintains its complement regulatory activities: it prohibits deposition of C4b, interferes with the assembly of the classical and lectin pathway C3-convertase and accelerates its decay (72) (Figure 2, 3).

*Candida albicans* has not only developed smart mechanisms to inactivate the complement attack, but also turns the hostile complement molecules into useful tools for its own purpose. In addition to downmodulation of the complement activity surface-attached C4bp mediates the adhesion of *Candida* to host endothelial cells (67, 73). Thus the capacity of *Candida* to acquire C4bp might represent an

important virulence factor for pathogenicity by facilitating the penetration into the host tissue. At present it is unclear which molecule(s) on endothelial cells act as receptor(s) for C4bp-coated *Candida*. CD40, a member of the TNF-receptor superfamily which is known to bind C4bp, might be a putative candidate (74). As C4bp was shown to adhere to heparin, the related cell surface molecule heparan sulfate is another aspirant (72).

*Candida* does not only acquire complement components from the host, but also expresses own proteins that mimic host-derived complement elements. A rather fascinating chapter of *Candida* virulence is the formation of complement receptor-like molecules on its surface. *C. albicans* expresses an integrin analogue with antigenic, structural and functional homology to human CR3 on both yeast and (pseudo)hyphal forms (75, 76, 77, 78). The human CR3 is essential for the adhesion of leukocytes via recognition of a peptide containing the sequence arginine-glycine-aspartic acid (RGD) in proteins of the extracellular matrix. Since the fungal CR3-like molecule shares essential homology to its human counterpart it can enable the adherence of *Candida* to endothelia and epithelia and thus represents an important virulence factor for penetration and dissemination. Several reports underline the role of CR3 for the pathogenesis of *Candida*. Blocking of the fungal CR3-like proteins by antibodies or defined RGD-peptides significantly inhibits the adherence to endothelia and epithelia (78, 79). A high production level of the fungal CR3-homologue is associated only with virulent strains of *C. albicans* while an avirulent mutant showed reduced synthesis (80). Furthermore, the expression of the cloned CR3-like molecule of *C. albicans* in *Saccharomyces cerevisiae* leads to the adhesion of this normally nonadherent yeast to human epithelial cells; the disruption of the responsible INT1 gene suppresses hyphal growth, adhesion to epithelial cells and virulence in mice (81, 82) (Figure 2, 3).

An additional role for the fungal CR3-like protein was proposed by Moors *et al.*: by binding *C. albicans* cells to erythrocytes it might help to acquire the life essential iron out of blood (83).

Besides the CR3-like molecule *C. albicans* also expresses a C3d-binding mannoprotein (84, 85, 86). A certain similarity to human CR2 is evident by cross-reacting antibodies, but the exact function of the fungal analogue remains obscure (87). Some evidence for a putative role of the C3d-receptor on *Candida* in pathogenesis comes from a mouse model where avirulent clones of *C. albicans* show reduced ability to recognize C3d and low reactivity with antibodies against the C3d-receptor in comparison to the virulent parental strain (88). Furthermore, immunoelectron microscopy as well as lymphoblastogenesis reveals that the CR2 analogue is expressed *in vivo* during candidiasis in animals (89, 90). A role of the C3d-receptor in binding to host fibrinogen and laminin may be suggested (91).

## 6. THE FIGHT “HOST AGAINST FUNGUS”, ROUND 3: FUTURE AND PERSPECTIVES

The current knowledge about the different aspects



of the interaction between *Candida* and the complement system allows some speculations about a future role of complement in antifungal treatment. Four strategies stand in the centre of putative therapeutic approaches (Figure 2): (i) to improve antifungal response by enhancing the available complement levels; (ii) to undermine *Candida*'s complement evasion and usage; (iii) to optimize the antibody reaction against *Candida* using complement-based tools; (iv) to use complement-derived peptides as supportive anti-*Candida* therapy.

(i) To increase the available complement concentrations was suggested for MBL, the starter molecule of the lectin pathway. Liu et al (24) reported that the susceptibility to recurrent vulvovaginal *Candida* infections is strongly associated with mutations in the MBL gene provoking low MBL levels in the vagina. Thus reconstitution of normal MBL levels by injection of purified or recombinant protein might represent an interesting strategy for therapy or prophylaxis. A phase I safety and pharmacokinetic study including MBL-deficient healthy volunteers showed that infusion of purified MBL increases the serum levels up to normal concentrations without induction of antibodies to MBL in these individuals (92). However, the short half-life of MBL asks for a twice or thrice weekly infusion to maintain protective MBL levels. This restriction largely excludes a long-standing routine usage in prophylaxis, except for some high risk patients. A proof of principle for MBL in prophylaxis could be shown in a mouse model where intravenous administration of MBL enhances the resistance of the animals towards hematogenously infected candidiasis (41). However, injection of MBL as a supportive therapy in *Candida*-infected patients may be the more probable broad application and more compatible with the limited stability of the protein.

(ii) A second possible therapeutic approach comprises the undermining of *Candida*'s complement evasion. The complement degradation by the *Candida*-secreted Sap2 protease (64) might be neutralized by usage of a specific protease inhibitor or monoclonal antibody or by inhibition of the synthesis of this protease, e.g. with short interfering RNAs (siRNA). Blocking of the acquisition of C4bp, fH and FHL-1 by *Candida* might be another possibility to make the yeast more susceptible against complement attack. For this purpose, however, the identification of the fungal binding sites is necessary, subsequently highly specific inhibitors against these molecules must be developed, since the blocking of the host receptors or the regulators themselves would have severe consequences for the immune defense. In this regard the inhibition of C4bp binding might be of particular interest, since it would also interfere with the adhesion of *Candida* to endothelial cells.

Interference with the fungal usage of complement-related proteins could also support the body's immune defense against *Candida*. The blocking of the fungal CR3-like proteins might provide an opportunity. Preliminary *in vitro* results show promise, demonstrating that receptor-specific antibodies or RGD-comprising peptides significantly inhibit the adherence of the yeast (78, 79). An approach like that should, however, pay attention to a putative cross-reaction of

these antibodies with the human CR3; RGD-peptides might be critical as well since this sequence is also used for a variety of human molecules.

(iii) As summarized above, the protective effect of antimannan antibodies against *Candida* infection strongly depends on their capacity to bind complement fragments to the yeast cells (38). This deposition can cause preferential association of *Candida* with phagocytic cells that are able to kill the yeast (37). This fact may be exploited for the development of an effective passive vaccination or as a supportive therapy against *Candida*. A monoclonal antibody given to high-risk patients as prophylaxis or applied in patients with known candidiasis should be optimized for an efficient induction of complement deposition on the fungal surface (47). Furthermore the susceptibility of high-risk patients against candidiasis might be tested by measurement of the capacity of their naturally occurring antimannan antibodies to fix complement of yeast cells.

(iv) The complement fragment C3a possesses prominent antifungal activity and can be utilized as a template in the development of a peptide-based therapy against *Candida*. C3a and derived peptides comprising its helical regions bind to the yeast and induce considerable membrane disturbances (58). Further studies might provide insight into the exact mechanism of action and allow the enhancement of the antifungal potency of the peptides by sequence variation.

## 7. ACKNOWLEDGEMENT

The authors are supported by the Österreichische Nationalbank (Project Nr. 11944), the State of Tyrol, and the Austrian BMAGS.

## 8. REFERENCES

1. Mavor A. L., S. Thewes & B. Hube: Systemic fungal infections caused by *Candida* species: epidemiology, infection process and virulence attributes. *Curr Drug Targets* 6(8), 863-874 (2005)
2. Pappas P. G.: Invasive candidiasis. *Infect Dis Clin North Am* 20(3), 485-506 (2006)
3. Sobel J.D.: Vulvovaginal candidosis. *Lancet* 369(9577), 1961-1971 (2007)
4. Fidel P. L. Jr.: Immunity to *Candida*. *Oral Dis* 8(Suppl2), 69-75 (2002)
5. Raska M., J. Běláková, M. Krupka & E. Weigl: Candidiasis-do we need to fight or to tolerate the *Candida* fungus? *Folia Microbiol (Praha)* 52(3), 297-312 (2007)
6. Speth C., C. Lass-Flörl & Reinhard Würzner: Complement in fungal infections and complement evasion strategies. In: Immunology of fungal infections. Eds: Brown G. D., Netea M. G., Springer, Dordrecht, The Netherlands (2007)
7. Goldfarb R. D. & J. E. Parrillo: Complement. *Crit Care Med* 33(Suppl), 482-484 (2005)
8. Proding W. M., R. Würzner, H. Stoiber & M. P. Dierich: Complement. In: Fundamental Immunology. Ed: Paul W. E., Lippincott, Philadelphia (2003)
9. Hugli T. E.: Structure and function of C3a anaphylatoxin. *Curr Top Microbiol Immunol* 153, 181-208 (1990)

10. Guo R. F. & P. A. Ward: Role of C5a in inflammatory responses. *Annu Rev Immunol* 23(1), 821-852 (2005)
11. Müller-Eberhard H. J.: The membrane attack complex of complement. *Annu Rev Immunol* 4, 503-528 (1986)
12. Petersen S. V., S. Thiel, L. Jensen, T. Vorup-Jensen, C. Koch & J. C. Jensenius: Control of the classical and the MBL pathway of complement activation. *Mol Immunol* 37(18), 803-811 (2000)
13. Krych-Goldberg M. & J. P. Atkinson: Structure-function relationships of complement receptor type 1. *Immunol Rev* 180(1), 112-122 (2001)
14. Fearon D. T. & M. C. Carroll: Regulation of B lymphocyte responses to foreign and self-antigens by the CD19/CD21 complex. *Annu Rev Immunol* 18, 393-422 (2000)
15. Chen Z., S. B. Koralov & G. Kelsoe: Regulation of the humoral immune responses by CD21/CD35. *Immunol Rev* 176, 194-204 (2000)
16. Ehlers M. R.: CR3: a general purpose adhesion-recognition receptor essential for innate immunity. *Microbes Infect* 2(3), 289-294 (2000)
17. Helmy K. Y., K. J. Katschke, N. N. Gorgani, N. M. Kljavin, J. M. Elliott, L. Diehl, S. J. Scales, N. Ghilardi & M. van Lookeren Campagne: CRIg: a macrophage complement receptor required for phagocytosis of circulating pathogens. *Cell* 124(5), 915-927 (2006)
18. Vogt L., N. Schmitz, M. O. Kurrer, M. Bauer, H. I. Hinton, S. Behnke, D. Gatto, P. Sebbel, R. R. Beerli, I. Sonderegger, M. Kopf, P. Saudan & M. F. Bachmann: VSIG4, a B7 family-related protein, is a negative regulator of T cell activation. *J Clin Invest* 116(10), 2817-2826 (2006)
19. Wiesmann C., K. J. Katschke, J. Yin, K. Y. Helmy, M. Steffek, W. J. Fairbrother, S. A. McCallum, L. Embuscado, L. DeForge, P. E. Hass & M. van Lookeren Campagne: Structure of C3b in complex with CRIg gives insights into regulation of complement activation. *Nature* 444(7116), 217-220 (2006)
20. Katschke K. J. Jr., K. Y. Helmy, M. Steffek, H. Xi, J. Yin, W. P. Lee, P. Gribling, K. H. Barck, R. A. Carano, R. E. Taylor, L. Rangell, L. Diehl, P. E. Hass, C. Wiesmann & M. van Lookeren Campagne: A novel inhibitor of the alternative pathway of complement reverses inflammation and bone destruction in experimental arthritis. *J Exp Med* 204(6), 1319-1325 (2007)
21. Gerard N. P. & C. Gerard: The chemotactic receptor for human C5a anaphylatoxin. *Nature* 349(6310), 614-617 (1991)
22. Gerard N. P., B. Lu, P. Liu, S. Craig, Y. Fujiwara, S. Okinaga & C. Gerard: An anti-inflammatory function for the complement anaphylatoxin C5a-binding protein, C5L2. *J Biol Chem* 280(48), 39677-39680 (2005)
23. Eggleton P., K. B. Reid & A. J. Tenner: C1q-how many functions? How many receptors? *Trends Cell Biol* 8(11), 428-431 (1998)
24. Liu F., Q. Liao & Z. Liu: Mannose-binding lectin and vulvovaginal candidiasis. *Int J Gynaecol Obstet* 92(1), 43-47 (2006)
25. Lukasser-Vogl E., A. Gruber, C. Lass-Flörl, A. Eder, A. K. Høgåsen, B. P. Morgan, M. P. Dierich & R. Würzner: Membrane attack complex formation on yeast as trigger of selective release of terminal complement proteins from human polymorphonuclear leukocytes. *FEMS Immunol Med Microbiol* 28(1), 15-23 (2000)
26. Babula O., G. Lazdane, J. Kroica, W. J. Ledger & S. S. Witkin: Relation between recurrent vulvovaginal candidiasis, vaginal concentrations of mannose-binding lectin, and a mannose-binding lectin gene polymorphism in latvian women. *Clin Infect Dis* 37(5), 733-737 (2003)
27. Giraldo P. C., O. Babula, A. K. Goncalves, I. M. Linhares, R. L. Amaral, W. J. Ledger & S. S. Witkin: Mannose-binding lectin gene polymorphism, vulvovaginal candidiasis, and bacterial vaginosis. *Obstet Gynecol* 109(5), 1123-1128 (2007)
28. Gelfand J. A., D. L. Hurley, A. S. Fauci & M. M. Frank: Role of complement in host defense against experimental disseminated candidiasis. *J Infect Dis* 138(1), 9-16 (1978)
29. Ray T. L. & K. D. Wuepper: Experimental cutaneous candidiasis in rodents; II. Role of the stratum corneum barrier and serum complement as a mediator of a protective inflammatory response. *Arch Dermatol* 114(4), 539-543 (1978)
30. Naked G. M., M. P. C. Florido, P. Ferreira de Paula, A. M. Vinet, J. S. Inostroza & L. Isaac: Deficiency of human complement factor I associated with lowered factor H. *Clin Immunol* 96(2), 162-167 (2000)
31. Kozel T. R., L. C. Weinhold & D. M. Lupan: Distinct characteristics of initiation of the classical and alternative complement pathways by *Candida albicans*. *Infect Immun* 64(8), 3360-3368 (1996)
32. Sohnle P. G., M. M. Frank & C. H. Kirkpatrick: Deposition of complement components in the cutaneous lesions of chronic mucocutaneous candidiasis. *Clin Immunol Immunopathol* 5(3), 340-350 (1976)
33. Sohnle P. G. & C. H. Kirkpatrick: Deposition of complement in the lesions of experimental cutaneous candidiasis in guinea pigs. *J Cutan Pathol* 3(5), 232-238 (1976)
34. Guhad F. A., H. E. Jensen & J. Hau: Complement activation in SCID and nude mice is related to severity of tissue inflammation in the *Candida* mastitis model. *FEMS Microbiol Lett* 192(1), 27-31 (2000)
35. Zhang M. X. & T. R. Kozel: Mannan-specific immunoglobulin G antibodies in normal human serum accelerate binding of C3 to *Candida albicans* via the alternative complement pathway. *Infect Immun* 66(10), 4845-4850 (1998)
36. Zhang M. X., J. E. Cutler, Y. Han & T. R. Kozel: Contrasting roles of mannan-specific monoclonal immunoglobulin M antibodies in the activation of classical and alternative pathways by *Candida albicans*. *Infect Immun* 66(12), 6027-6029 (1998)
37. Han Y., T. R. Kozel, M. X. Zhang, R. S. McGill, M. C. Carroll & J. E. Cutler: Complement is essential for protection by an IgM and an IgG3 monoclonal antibody against experimental, hematogenously disseminated candidiasis. *J Immunol* 167(3), 1550-1557 (2001)
38. Cutler J. E.: Defining criteria for anti-mannan antibodies to protect against candidiasis. *Curr Mol Med* 5(4), 383-392 (2005)
39. Xin H. & J. E. Cutler: Hybridoma passage in vitro may result in reduced ability of antimannan antibody to protect against disseminated candidiasis. *Infect Immun* 74(7), 4310-4321 (2006)

40. Kozel T. R., R. S. McGill, A. Percival & Q. Zhou: Biological activities of naturally occurring antibodies reactive with *Candida albicans* mannan. *Infect Immun* 72(1), 209-218 (2004)
41. Lillegard J. B., R. B. Sim, P. Thorkildson, M. A. Gates & T. R. Kozel: Recognition of *Candida albicans* by mannan-binding lectin in vitro and in vivo. *J Infect Dis* 193(11), 1589-1597 (2006)
42. Ip W. K. & Y. L. Lau: Role of mannose-binding lectin in the innate defense against *Candida albicans*: enhancement of complement activation, but lack of opsonic function, in phagocytosis by human dendritic cells. *J Infect Dis* 190(3), 632-640 (2004)
43. Pellis V., F. De Seta, S. Crovella, F. Bossi, R. Bulla, S. Guaschino, O. Radillo, P. Garred & F. Tedesco: Mannose binding lectin and C3 act as recognition molecules for infectious agents in the vagina. *Clin Exp Immunol* 139(1), 120-126 (2005)
44. Zhang M. X., D. M. Lupan & T. R. Kozel: Mannan-specific immunoglobulin G antibodies in normal human serum mediate classical pathway initiation of C3 binding to *Candida albicans*. *Infect Immun* 65(9), 3822-3827 (1997)
45. Kozel T. R.: Activation of the complement system by pathogenic fungi. *Clin Microbiol. Rev.* 9(1), 34-46 (1996)
46. Gruber A., E. Lukasser-Vogl, M. Borg-von Zepelin, M. P. Dierich & R. Würzner: Human immunodeficiency virus type 1 gp160 and gp41 binding to *Candida albicans* selectively enhances candidal virulence in vitro. *J Infect Dis* 177(4), 1057-1063 (1998)
47. Zhang M. X., M. C. Bohlmann, C. Itatani, D. R. Burton, P. W. H. I. Parren, S. C. St. Jeor & T. R. Kozel: Human recombinant antimannan immunoglobulin G1 antibody confers resistance to hematogenously disseminated candidiasis in mice. *Infect Immun* 74(1), 362-369 (2006)
48. Pereira H. A. & C. S. Hosking: The role of complement and antibody in opsonization and intracellular killing of *Candida albicans*. *Clin Exp Immunol* 57(2), 307-14 (1984)
49. Szabo I., L. Guan & T. J. Rogers: Modulation of macrophage phagocytic activity by cell wall components of *Candida albicans*. *Cell Immunol* 164(2), 182-188 (1995)
50. Andrews T. & K. E. Sullivan: Infections in patients with inherited defects in phagocytic function. *Clin Microbiol Rev* 16(4), 597-621 (2003)
51. Forsyth C. B. & H. L. Mathews: Lymphocytes utilize CD11b/CD18 for adhesion to *Candida albicans*. *Cell Immunol* 170(1), 91-100 (1996)
52. Forsyth C. B., E. F. Plow & L. Zhang: Interaction of the fungal pathogen *Candida albicans* with integrin CD11b/CD18: recognition by the I domain is modulated by the lectin-like domain and the CD18 subunit. *J Immunol* 161(11), 6198-6205 (1998)
53. Lavigne L. M., J. E. Albina & J. S. Reichner: Beta-glucan is a fungal determinant for adhesion-dependent human neutrophil functions. *J Immunol* 177(12), 8667-8675 (2006)
54. Forsyth C. B. & H. L. Mathews: Lymphocyte adhesion to *Candida albicans*. *Infect Immun* 70(2), 517-527 (2002)
55. Romani L., C. Montagnoli, S. Bozza, K. Perrucione, A. Spreca, P. Allavena, S. Verbeek, R. A. Calderone, F. Bistoni & P. Puccetti: The exploitation of distinct recognition receptors in dendritic cells determines the full range of host immune relationships with *Candida albicans*. *Int Immunol* 16(1), 149-161 (2004)
56. Triebel T., B. Grillhösl, L. Kacani, C. P. Lell, A. Fuchs, C. Speth, C. Lass-Flörl, J. Steinmann, M. P. Dierich & R. Würzner: Importance of the terminal complement components for immune defence against *Candida*. *Int J Med Microbiol* 37(5), 527-536 (2003)
57. Ghezzi M. C., G. Raponi, S. Angeletti & C. Mancini: Serum-mediated enhancement of TNF-alpha release by human monocytes stimulated with the yeast form of *Candida albicans*. *J Infect Dis* 178(6), 1743-1749 (1998)
58. Sonesson A., L. Ringstad, E. A. Nordahl, M. Malmsten, M. Mörgelin & A. Schmidtchen: Antifungal activity of C3a and C3a-derived peptides against *Candida*. *Biochim Biophys Acta* 1768(2), 346-358, (2007)
59. Mullick A., M. Elias, S. Picard, L. Bourget, O. Jovceviski, S. Gauthier, A. Tuite, P. Harakidas, C. Bihun, B. Massie & P. Gros: Dysregulated inflammatory response to *Candida albicans* in a C5-deficient mouse strain. *Infect Immun* 72(10), 5868-5876 (2004)
60. Tuite A., M. Elias, S. Picard, A. Mullick & P. Gros: Genetic control of susceptibility to *Candida albicans* in susceptible A/J and resistant C57BL/6J mice. *Genes Immun* 6(8), 672-682 (2005)
61. Mullick A., Z. Leon, G. Min-Oo, J. Berghout, R. Lo, E. Daniels & P. Gros: Cardiac failure in C5-deficient A/J mice after *Candida albicans* infection. *Infect Immun* 74(8), 4439-4451 (2006)
62. Würzner R.: Evasion of pathogens by avoiding recognition or eradication by complement, in part via molecular mimicry. *Mol Immunol* 36(4-5), 249-260 (1999)
63. Monod M., S. Capoccia, B. Lechenne, C. Zaugg, M. Holdom & O. Jousson: Secreted proteases from pathogenic fungi. *Int J Med Microbiol* 292(5-6), 405-419 (2002)
64. Kaminishi H., H. Miyaguchi, T. Tamaki, N. Suenaga, M. Hisamatsu, I. Mihashi, H. Matsumoto, H. Maeda & Y. Hagihara: Degradation of humoral host defense by *Candida albicans* proteinase. *Infect Immun* 63(3), 984-988 (1995)
65. Naglik J.R., S.J. Challacombe & B. Hube: *Candida albicans* secreted aspartyl proteinases in virulence and pathogenesis. *Microbiol Mol Biol Rev* 67(3), 400-428 (2003)
66. Lian C. H. & W. D. Liu: Differential expression of *Candida albicans* secreted aspartyl proteinase in human vulvovaginal candidiasis. *Mycoses* 50(5), 383-390 (2007)
67. Blom A. M.: Strategies developed by bacteria and virus for protection from the human complement system. *Scand J Clin Lab Invest* 64(5), 479-496 (2004)
68. Kirkitaдзе M. D. & P. N. Barlow: Structure and flexibility of the multiple domain proteins that regulate complement activation. *Immunol Rev* 180, 146-161 (2001)
69. Zipfel P. F., R. Würzner & C. Skerka: Complement evasion of pathogens: Common strategies are shared by diverse organisms. *Mol Immunol* 44(16), 3850-3857 (2007)
70. DiScipio R. G., P. J. Daffern, I. U. Schraufstatter & P. Sriramarao: Human polymorphonuclear leukocytes adhere to complement factor H through an interaction that involves alphaMbeta2 (CD11b/CD18). *J Immunol* 160(8), 4057-4066 (1998)
71. Meri T., A. Hartmann, D. Lenk, R. Eck, R. Würzner, J. Hellwage, S. Meri & P. F. Zipfel: The yeast *Candida albicans* binds complement regulators factor H and FHL-1. *Infect Immun* 70(9), 5185-51192 (2002)

72. Blom A. M., B. O. Villoutreix & B. Dahlbäck: Complement inhibitor C4b-binding protein-friend or foe in the innate immune system? *Mol Immunol* 40(18), 1333-1346 (2004)
73. Meri T., A. M. Blom, A. Hartmann, D. Lenk, S. Meri & P. F. Zipfel: The hyphal and yeast forms of *Candida albicans* bind the complement regulator C4b-binding protein. *Infect Immun* 72(11), 6633-6641 (2004)
74. Brodeur S. R., F. Angelini, L. B. Bacharier, A. M. Blom, E. Mizoguchi, H. Fujiwara, A. Plebani, L. D. Notarangelo, B. Dahlback, E. Tsitsikov & R. S. Geha: C4b-binding protein (C4BP) activates B cells through the CD40 receptor. *Immunity* 18(6), 837-848 (2003)
75. Gilmore B. J., E. M. Retsinas, J. S. Lorenz & M. K. Hostetter: An iC3b receptor on *Candida albicans*: structure, function, and correlates for pathogenicity. *J Infect Dis* 157(1), 38-46 (1988)
76. Eigentler A., T. F. Schulz, C. Larcher, E. M. Breitwieser, B. L. Myones, A. L. Petzer & M. P. Dierich: C3bi-binding protein on *Candida albicans*: temperature-dependent expression and relationship to human complement receptor type 3. *Infect Immun* 57(2), 616-622 (1989)
77. Hostetter M. K., J. S. Lorenz, L. Preus & K. E. Kendrick: The iC3b receptor on *Candida albicans*: subcellular localization and modulation of receptor expression by glucose. *J Infect Dis* 161(4), 761-768 (1990)
78. Gustafson K. S., G. M. Vercellotti, C. M. Bendel & M. K. Hostetter: Molecular mimicry in *Candida albicans*. Role of an integrin analogue in adhesion of the yeast to human endothelium. *J Clin Invest* 87(6), 1896-1902 (1991)
79. Bendel C. M. & M. K. Hostetter: Distinct mechanisms of epithelial adhesion for *Candida albicans* and *Candida tropicalis*. Identification of the participating ligands and development of inhibitory peptides. *J Clin Invest* 92(4), 1840-1809 (1993)
80. Ollert M. W., E. Wadsworth & R. A. Calderone: Reduced expression of the functionally active complement receptor for iC3b but not for C3d on an avirulent mutant of *Candida albicans*. *Infect Immun* 58(4), 909-913 (1990)
81. Gale C., D. Finkel, N. Tao, M. Meinke, M. McClellan, J. Olson, K. Kendrick & M. Hostetter: Cloning and expression of a gene encoding an integrin-like protein in *Candida albicans*. *Proc Natl Acad Sci USA* 93(1), 357-361 (1996)
82. Gale C. A., C. M. Bendel, M. McClellan, M. Hauser, J. M. Becker, J. Berman & M. K. Hostetter: Linkage of Adhesion, Filamentous Growth, and Virulence in *Candida albicans* to a Single Gene, INT1. *Science* 279(5355), 1355-1358 (1998)
83. Moors M. A., T. L. Stull, K. J. Blank, H. R. Buckley & D. M. Mosser: A role for complement receptor-like molecules in iron acquisition by *Candida albicans*. *J Exp Med* 175(6), 1643-1651 (1992)
84. Heidenreich F. & M. P. Dierich: *Candida albicans* and *Candida stellatoidea*, in contrast to other *Candida* species, bind iC3b and C3d but not C3b. *Infect Immun* 50(2), 598-600 (1985)
85. Linehan L., E. Wadsworth & R. Calderone: *Candida albicans* C3d receptor, isolated by using a monoclonal antibody. *Infect Immun* 56(8), 1981-1986 (1988)
86. Saxena A. & R. Calderone: Purification and characterization of the extracellular C3d-binding protein of *Candida albicans*. *Infect Immun* 58(2), 309-314 (1990)
87. Edwards J. E. Jr., T. A. Gaither, J. J. O'Shea, D. Rotrosen, T. J. Lawley, S. A. Wright, M. M. Frank & I. Green: Expression of specific binding sites on *Candida* with functional and antigenic characteristics of human complement receptors. *J Immunol* 137(11), 3577-3583 (1986)
88. Franzke S., R. A. Calderone & K. Schaller: Isolation of avirulent clones of *Candida albicans* with reduced ability to recognize the CR2 ligand C3d. *Infect Immun* 61(6), 2662-2669 (1993)
89. Kanbe T., R. K. Li, E. Wadsworth, R. A. Calderone & J. E. Cutler: Evidence for expression of the C3d receptor of *Candida albicans* in vitro and in vivo obtained by immunofluorescence and immunoelectron microscopy. *Infect Immun* 59(5), 1832-1838 (1991)
90. Fukayama M., E. Wadsworth & R. Calderone: Expression of the C3d-binding protein (CR2) from *Candida albicans* during experimental candidiasis as measured by lymphoblastogenesis. *Infect Immun* 60(1), 8-12 (1992)
91. Tronchin G., J. P. Bouchara & R. Robert: Dynamic changes of the cell wall surface of *Candida albicans* associated with germination and adherence. *Eur J Cell Biol* 50(2), 285-290 (1989)
92. Valdimarsson H., T. Vikingsdottir, P. Bang, S. Saevarsdottir, J. E. Gudjonsson, O. Oskarsson, M. Christiansen, L. Blou, I. Laursen & C. Koch: Human plasma-derived mannose-binding lectin: a phase I safety and pharmacokinetic study. *Scand J Immunol* 59(1), 97-102 (2004)

**Abbreviations:** C4bp: c4 binding protein, CD: cluster of differentiation, CR: complement receptor, CRiG (complement receptor of the immunoglobulin superfamily), CVF: cobra venom factor, DAF: decay accelerating factor, DC: dendritic cell, Fc: constant portion (fragment) of the immunoglobulin molecule, FDC: follicular dendritic cells, fH: factor H, FHL-1: factor H-like protein 1, fI: factor I, HIV: human immunodeficiency virus, ICAM: intercellular adhesion molecule, Ig: immunoglobulin, MAC: membrane attack complex, MASP: MBL-associated serine protease, MBL: mannan-binding lectin, MCP: membrane cofactor protein, PAMP: pathogen-associated molecular pattern, PGE2: prostaglandin E2, PMN: polymorphonuclear leukocyte, RGD: arginine-glycine-aspartic acid, Sap: secreted aspartic protease, siRNA: short interfering RNA, SCR: short consensus repeat, TCC: terminal complement complex, TNF: tumor necrosis factor, VSIG4: V-set and Ig domain-containing (protein) 4

**Key Words:** *Candida albicans* Infections, Candidiasis, Complement System, Innate Immunity, Antifungal Complement Functions, Complement Evasion, Molecular Mimicry, Therapy, Review

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