The fungus *Candida albicans* can be considered part of our normal flora and is found in up to 80% of all individuals. It colonizes the oral cavity, gastrointestinal tract, vagina, and intertriginous regions, such as those in the inguinal area. Infections or overgrowth with *C. albicans* are commonly seen. Most of these episodes, such as oral candidiasis (ie, thrush) in newborns, are benign, fortunately. However, *C. albicans* is the fourth most common species isolated from patients with nosocomial sepsis, after coagulase-negative staphylococci, *Staphylococcus aureus*, and enterococci [1]. Patients with urinary catheters, individuals receiving broad-spectrum antibiotics, and immunocompromised hosts are more susceptible than others to infections caused by *C. albicans*. The latter group is increasing in size and includes transplant recipients who are receiving immunosuppressive treatment and neutropenic patients with cancer [2]. Moreover, patients with T-cell deficiencies and defects in phagocytic killing, such as individuals with AIDS and chronic granulomatous disease, respectively, are at risk for infections with *C. albicans*. Another troublesome clinical condition is chronic mucocutaneous candidiasis, which is secondary to various underlying medical diseases, including impaired T-cell function related to dysfunction in interleukin 17 immunity [3]. Thus, there is an urgent need for us to learn more about *C. albicans* colonization and disease in order to effectively keep these organisms in check.

Our barrier against the world around us consists, in part, of sophisticated humoral defense systems found in the epidermal and mucosal tissues. Antimicrobial peptides, immunoglobulins, and the complement system are all very important, in addition to the cellular immune system. The complement system is part of the innate immune system, which recognizes molecular patterns displayed by different microbes. It is activated via 3 different pathways, and the well-known classical pathway of complement activation plays a major role, because it is initiated by C1q bound to antibodies targeted against specific microbes [4]. In addition, the lectin pathway is initiated by mannann-binding lectins, and both of these pathways lead to activation of C3, resulting in the C3 convertase. In parallel, the alternative pathway is triggered by spontaneous deposition of the C3b molecule at the microbial surface, leading to C3 convertase. All 3 pathways merge via C5 convertase and are finalized in the terminal pathway of complement activation, resulting in the terminal complement complex, also known as the membrane attack complex, consisting of C5b to C9, which subsequently drills holes in the microbial cell membrane.

It is extraordinarily important for the human host to keep the complement system tightly controlled in order to avoid tissue damage. In addition to cellular receptors (eg, CD46 and CD55), this control is achieved for the classical and lectin pathways by a series of fluid phase inhibitors, including C4b binding protein and C1 inhibitor [4]. Factor H, FH-like protein 1 (FHL-1), and properdin are inhibitors that keep track of the alternative pathway, whereas complement factor H-related protein 1, clusterin, and vitronectin regulate the formation of the membrane attack complex and are thus important inhibitors of the terminal pathway.

In recent years, several microbial proteins, both from the outer membrane and the cytoplasm, have been shown to bind host factors, such as complement regulators factor H and C4b binding protein [4, 5]. In fact, it can be anticipated that the vast majority of microbes...
have more or less specific receptors for numerous complement regulators. A particular pathogen can also present several receptors that attract the same ligand but with different affinities. This phenomenon is exemplified by the respiratory pathogen Haemophilus influenzae, which binds vitronectin with both Haemophilus surface fibrils and protein E [6, 7]. Intriguingly, H. influenzae protein E also simultaneously binds laminin and vitronectin [8]. The adhesin Moraxella catarrhalis ubiquitous surface protein A1 (UspA1) belongs to another well-examined family of multifunctional outer membrane proteins interacting with the host and its immune system [9]. UspA1 and UspA2 have binding sites for C4b binding protein and vitronectin, in addition to fibronectin, laminin, antichymotrypsin, and CAECAM1. Furthermore, UspA2 neutralizes C3d, resulting in a highly serum resistant species. M. catarrhalis, armored with the UspAs, thus survives as a commensal in the mucosa. This interesting way of inhibiting the alternative pathway also plays a role in the interaction between M. catarrhalis and other microbes. We found that the relatively serum-susceptible H. influenzae is protected by outer membrane vesicles (nanoparticles) derived from M. catarrhalis. Outer membrane vesicles neutralize C3d and, thus, inhibit the complement activation at a distance, like a cluster bomb launched from the bacterium, protecting both bacterial species from the deleterious complement-mediated killing [10].

Another strategy to overcome the innate immune system is to degrade complement directly. This degradation is performed by bacteria dwelling in the oral cavity. For example, Tannerella forsythia has a very powerful metalloproteinase (kariysin) that directly degrades several complement proteins [11].

Plasminogen is found in the bloodstream as a zymogen and is, on activation, converted to the protease plasmin by interactions with tissue plasminogen activator and urokinase plasminogen activator [12]. The main target of plasmin is fibrin, resulting in fibrinolysis that keeps hemostasis at balance. Plasminogen is tightly controlled by inhibitors, such as plasminogen activator inhibitor 1 and 2, among others [8]. Microbes have numerous immune evasion strategies, and some have the capability to degrade plasminogen activator inhibitor by using specific proteases, in addition to the ability to attract plasminogen directly and, thus, convert it to plasmin. All of these different mechanisms lead to destruction of the extracellular matrix (including laminin), allowing subsequent invasion. Several different pathogens use plasminogen and plasmin for their survival in the host, and examples of common bacteria are the gram-positive organisms Staphylococcus aureus and Streptococcus pneumoniae and the gram-negative organisms H. influenzae and Borrelia burgdorferi.

C. albicans also has an array of different strategies to survive in the host [13]. The species is equipped with a thick cell wall that partly resists attacks from the immune system. However, its pathogen-associated molecular patterns are recognized by several Toll-like receptors and C-type lectin receptors. C. albicans β-glucans activate immune cells via the cell receptor dectin 1, and mannosyl residues are targets for efficient opsonization and phagocytosis. Interestingly, C. albicans also releases aspartic protease that disarms C3b, preventing opsonization [14].

In the article by Luo and collaborators in this issue of the Journal, factor H–coupled sepharose was used to isolate glycerol-3-phosphate dehydrogenase 2 (Gpd2), a novel factor H–binding protein of C. albicans [15]. Interestingly, Gpd2 also attracts FHL-1 and plasminogen, and it mediates binding to nonphagocytic cells (ie, endothelial and epithelial cells). In general, bacteria and fungi use numerous backup mechanisms for optimal interaction(s) with the host innate immune system, both humoral and cellular arms, and epithelial cell barriers. C. albicans is not an exception; the fungus binds factor H with 3 other proteins: phosphoglycerate mutase 1/ complement regulator–acquiring surface protein 1 (CRASP1), pH-regulated antigen 1/CRASP2 (Pra1/CRASP2), and Hgt1p [16]. The 2 former proteins have been shown to also interact with FHL-1 and plasminogen. In addition, one of these outer membrane proteins, Pra1/CRASP2, binds C4b binding protein and C3 [17]. Gpd2 is expressed both on the C. albicans surface and hyphae [15]. The target sequence was shown to be within short consensus repeat (SCR) 7 in factor H and FHL-1, a SCR that is shared with Streptococcus pyogenes [18] and, partly, with H. influenzae, among others [19]. In contrast, S. pneumoniae binds both to SCRs 8–11 and SCRs 12–15 [5]. Despite Gpd2-dependent binding to factor H and FHL-1, the 2 complement regulatory proteins were able to cleave C3b. In parallel, Gpd2-bound plasminogen was accessible for urokinase plasminogen activator, resulting in plasmin generation and, consequently, fibrinogen degradation.

It is intriguing how pathogens can use a cytoplasmic protein for several purposes. C. albicans Gpd2 is a nicotinamide adenine dinucleotide–dependent enzyme that plays a role in glycerol metabolism in the cytoplasm but also attracts complement regulators at the surface. An interesting parallel is the cytoplasmically located protein elongation factor Tuf from P. aeruginosa, which binds both factor H and plasminogen at the bacterial surface [20].

A clinically important example highlighting newly gained knowledge regarding complement regulators is the recently developed vaccine against meningococcus group B (4CMenB), which includes the highly immunogenic Neisseria meningitidis factor H–binding protein [21]. From a vaccine point of view, it is useful to target microbial proteins that bind complement regulators such as factor H. However, since most pathogens also have backup mechanisms for combating the host complement system, we cannot just rely on a single protein; we need multicomponent vaccines. Because we consider C. albicans as a part of our
normal flora, we should most likely not immunize against this species. However, proteins attracting complement regulators and plasminogen, such as *C. albicans* Gpd2, might be useful targets for intervention. Since the incidence of fungal infections is steadily increasing, more research is required in defining efficient future therapies, and the article by Luo et al [15] is an interesting step in that direction.

**Notes**

**Financial support.** This work was supported by the Alfred Osterlund Foundation, the Anna and Edwin Berger Foundation, the Greta and Johan Kock Foundation, the Swedish Research Council, the Swedish Society of Medicine, the Cancer Foundation at the University Hospital in Malmö, and the Skåne County Council Research and Development Foundation.

**Potential conflicts of interest.** Author certifies no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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