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Candida and Candidiasis - A review article of Virulence Factors

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Abstract

The occurrences of invasive candidiasis has increased over the previous few decades. Although *Candida albicans* considers as one of the most common species of organisms, that cause acquired fungal infections.

***Candida albicans* is an opportunistic fungal pathogen and inherent in as a lifelong, the yeast is present in healthy individuals as a commensal, and can reside harmlessly in human body. However, in immuno-compromised individuals, the fungus can invade tissues, producing superficial infections and, in severe cases, life-threatening systemic infections. This review wills emphasis on virulence factor of *C. albicans* including (adhesion, invasion, candida proteinase, and phenotypic switching and biofilm formation.**

Invasive Fungal diseases are result in very high morbidity as well as up to 60% mortality for people with severely susceptible hosts. This review will illustrate briefly the virulence factors in *Candida albicans.*

Keywords: *Candida albicans*, virulence factors, candidiasis.

Introduction

Candida albicans is a commensal organism, (normal flora) exist in our gastrointestinal and oral cavity. It is an opportunistic pathogen that colonies different niche in human. Candida can cause life-threating infections especially with immune-suppressed patients. (1) (2)

The pathogenesis of candidiasis can be contributed from expression of various virulence factors like phenotypic switching from yeast to hyphae, adhesion and biofilm formation and secretion of hydrolytic enzymes.

Candida requires several virulence factors to invade the host tissue beginning with adhesion, yeast-hyphae transition and secreted hydrolyses to infect the tissue. (3) Innate immune cells act as mediators to attack microorganisms by phagocytosis. Macrophages and neutrophils are main effector cells that reside in target tissues and organs in order to damage or kill invading fungi via phagocytosis. The antifungal effector cells release antimicrobials such as Reactive Oxygen Species (ROS) or secreting inflammatory signal such as cytokines and chemokines, which are essential to recruit additional immune response cells to the site of infection.

The fungal cell wall is the first point of contact with innate immune cells; thus, it plays an important role in the immune response. The polysaccharide core of the fungal cell wall is highly immunogenic; leading to rapid detection and recognition by innate immune cells especially neutrophils and macrophages. (4)

On the other hand, with the immunocompromised patients, some members of the normal flora, such as *C. albicans*, can cause systematic infections by invading and crossing the host's protective barriers and colonize every niche causing life-threatening conditions. (8) Oral mucosal infections, characterized by Candida overgrowth linked with an innate immune response, are remarkably common and have an affected on health, which is related the quality of our life. (Fig. 1).

C. *albicans* commensalism

Systemic infections in humans are often caused by microbiome–organisms like bacterial or fungal species that normally residing a different locale in our body, particularly oral cavity or mucosal surfaces. (5) Therefore, a hallmark of *C. albicans* is their aptitude to colonize several niches within the host. (6) Our skin, mouth, oral cavity and gastrointestinal tracts, in addition to our genital are laden with microorganisms. Most of them are commensal microorganisms, which as harmless and provide advantages to humans. (7)

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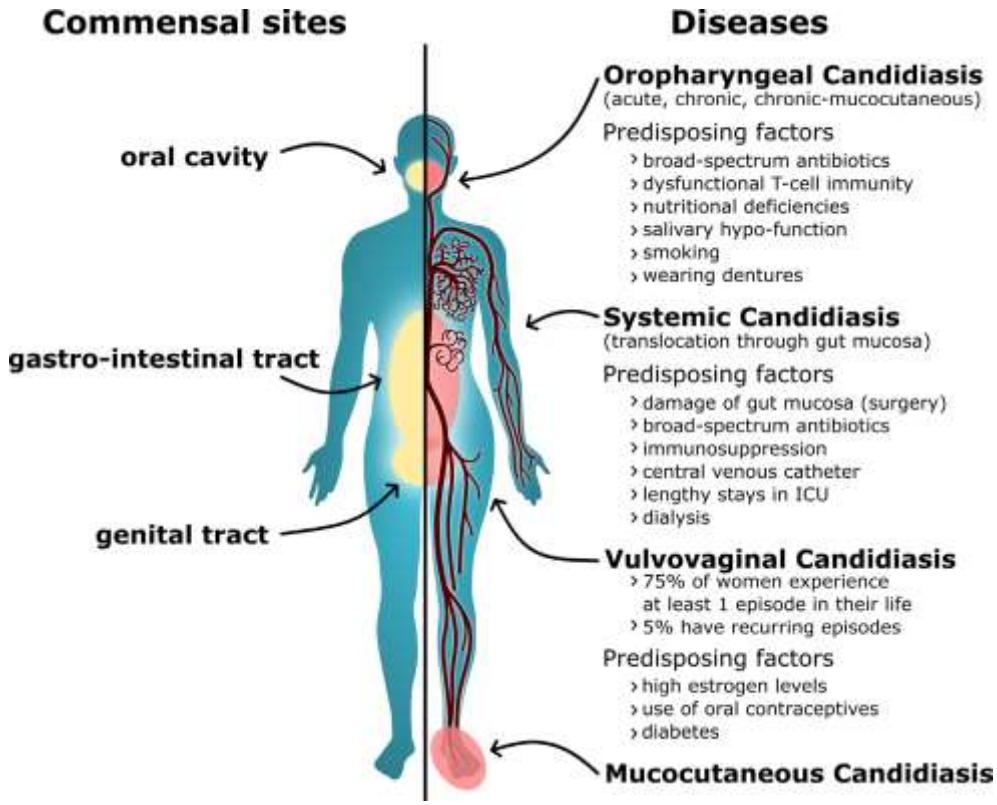

Figure 1. *C. albicans* commensalism and disease locations on the human body. (8)

Candida has versatility as a pathogen, and adapts as a commensal to various anatomically distinct sites in human body. (9) *C. albicans* opportunism includes the oral cavity, gastrointestinal tract and the genital tract. *C. albicans* can infect these sites to cause diseases (candidiasis). It also causes mucocutaneous and superficial infections (i.g. skin and nail). Meanwhile, *C. albicans* can also cause systemic infections, which often arise *via* translocation and dissemination of *C. albicans* from the gastrointestinal tract into the bloodstream.

Undoubtly, the understanding about the factors and conditions that enhance *C. albicans* commensalism or opportunism is essential to illustrate the mechanisms that underlie the switching from commensalism to pathogenicity. In fact, the pathogenicity of *Candida albicans* is mediated by impairing a host's resistance to infection, locally or systemically. (9) Candida species has the ability to cause different types of infection by regulation the expression of its virulence factors and fitness attributes to the different niche of human body. (10)

Pathogenicity and Virulence factors

C. albicans has the ability to cause infections that range from superficial infections of the skin to life-threatening systemic infections. Understanding the pathogenicity of *C. albicans* is essential to develop new therapies and diagnostic antifungal. (11)

Polymorphism

C. albicans, has four major cellular morphologies, namely yeast cells, pseudohyphae, hyphae, and chlamydospores. These polymorphisms differences between the forms of the growth of *C. albicans* affect the pathogenicity of the fungus. (12) Candida is able to regulate cellular morphogenesis, which is associated with the composition and architecture of the cell wall; this can recognize by the host immune system. Certain conditions can lead fungal cell to grow as yeast or hyphae, and the capability to switch from one form to another in response to external references is rapid. (13) The switching is facilitated by particular conditions; nutrients, a temperature of 37-40°C, pH, CO2 concentrations of approximately 5.5%, and some

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amino acids. This transition is a requisite for pathogenicity. Yeast forms are more suitable for dissemination in the host tissues, while filamentous forms are required for invading the tissues. Filamentous forms have a powerful ability for adherence and greater invasiveness of the host tissues. (14)

Adhesion and invasion

C. albicans is a pathogen that is known for its capability to utilize two distinct mechanisms: induced endocytosis and active penetration (15) (16)
(Fig. 2)

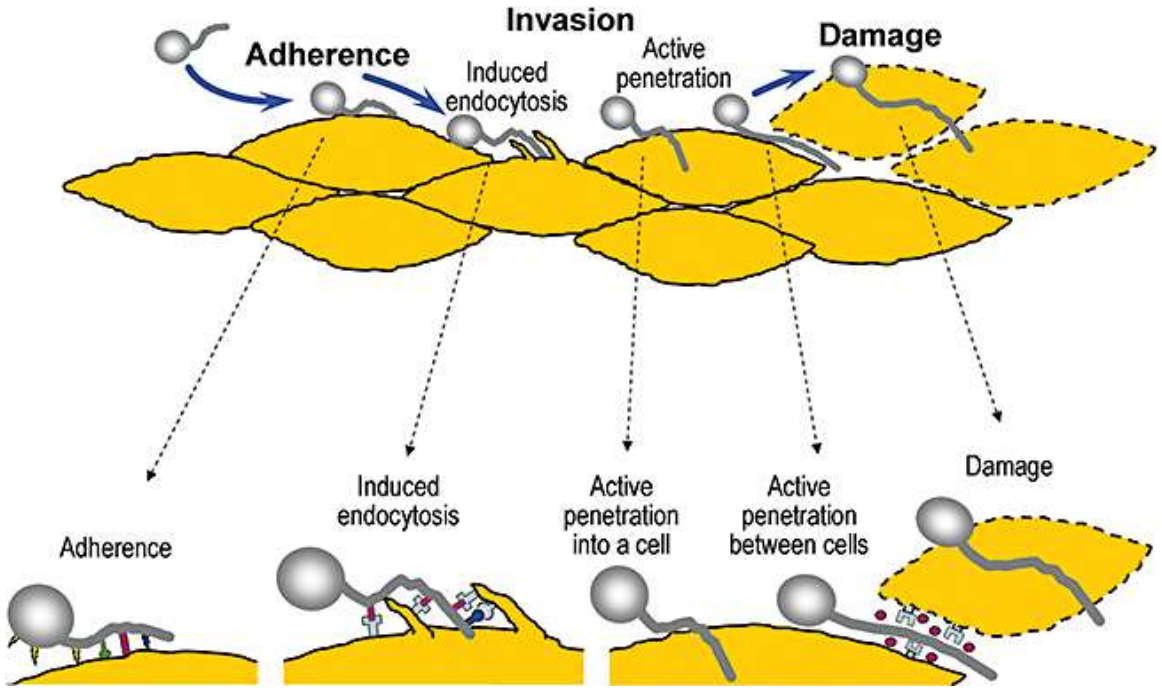

Figure 2. Fungal invasion - An overview of induced endocytosis and active penetration. (33)

Candida cells are notable to adhere to each host cells by specific adhesins such as such als1-7, als9, hwp1, eap1, and pga1, as well as penetrate and degrade the mucosal tissue and vascular barriers. *C. albicans* can also invade epithelial cells utilizing the mechanism of inducing epithelial cell endocytosis, which is controlled by Mitogen-activated protein (MAP) kinases. It can excite a switch from yeast cells to a hypha form. (17)

In addition, Candida cells promote the production of pseudopods by cells, which engulf Candida cell and pull them inside host tissues. This mechanism requires binding to the epithelial cell surface proteins and is dependent on the active participation of the pathogen – since this route does not take up dead cells. (15)

In fact, invasion via filamentous form of *C. albicans* not only depends on fungal viability and morphology, but also the type of anatomical site of human body. (15) (16) (18)

Secreted hydrolases

Hydrolytic enzymes are extracellular secreted and the most important enzymes that are responsible for Candida virulence factors and causing pathogenicity (Fig. 3). The enzymes affect *C. albicans* invasion and degradation host proteins such as hemoglobin and keratin as well as alter the structure of the cell membrane in order to facilitate invasion, and host attack by targeting cells of the host's immune system and avoidance of antimicrobial agents. This process occurs not only in *C. albicans*, but also in other Candida species (eg. *C. parapsilosis, C. tropicalis* and *C. dubliniensis* (19) (20) (21)(22)

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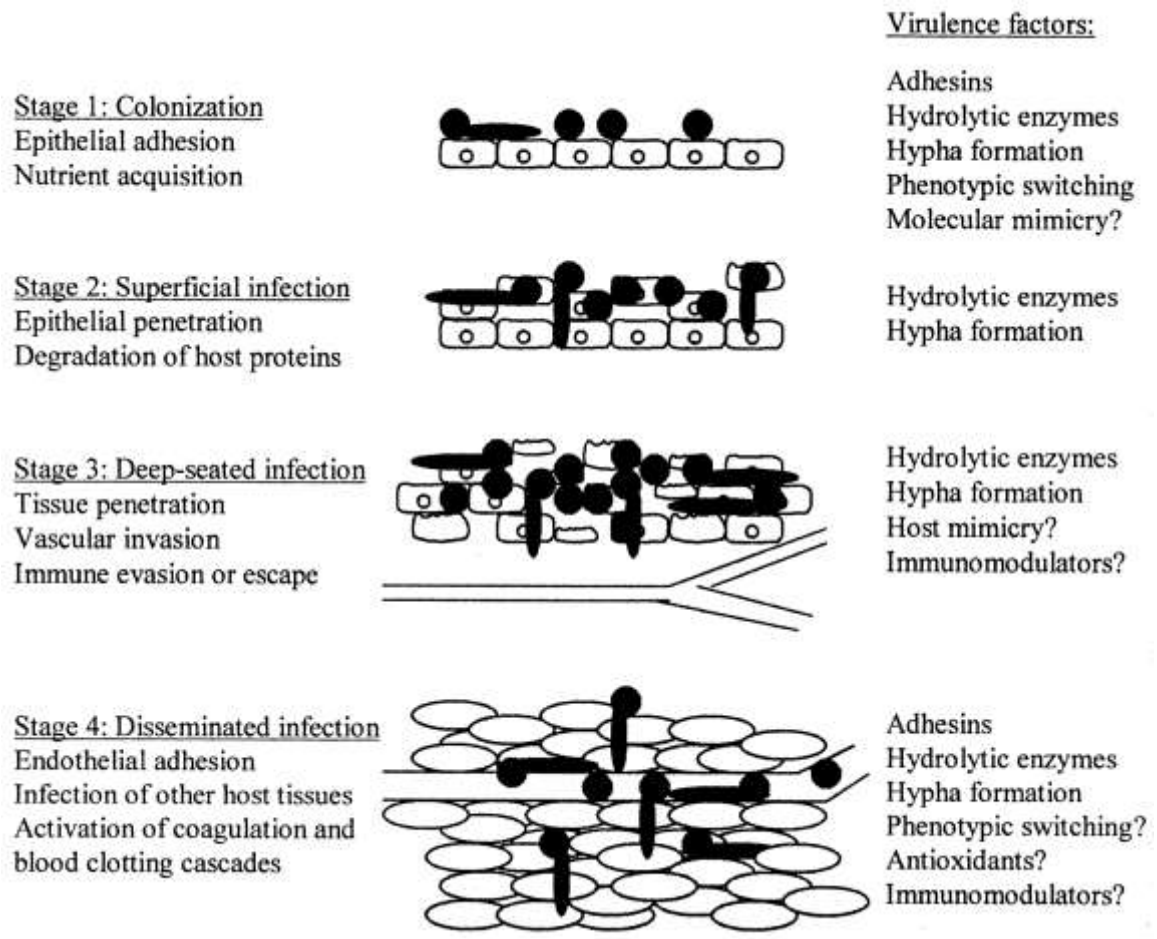

Figure 3. Diagram illustrate the contribution of different virulence attributes to *C.* pathogenicity. (32)

pH sensing and metabolic adaptation of Candida

Many researches have reported that Candida has high ability to adapt sense and grow within different environmental conditions and within distinct niches that exhibit different pHs. This tolerance is important for pathogenicity of *C. albicans*. Generally, pathogenicity of Candida can occur by encountering highly broad of pHs conditions (pH -2) in stomach. In addition, Candida can directly alter pH condition to mildly neutral and alkaline environment elsewhere because growth of Candida is very poorly at alkaline pH. This highly efficiency of Candida resulting in the inducing transition of Candida cells. (23) (22) The metabolic adaptation of *Candida albicans*, is an essential factor in a medical field because of its capacity to occupy diverse sites in the human host. In general, human niches contain many different types of assimilable and non-assimilable carbon sources. *C. albicans* has the ability to grow and assimilate many of these carbon sources but mainly favours glucose. (24) To grow well within different human niches, Candida can exhibit notable metabolic flexibility in human body.

Biofilm formation

Fungal biofilm formation is a complex process that is highly organized structure, which is distinct by adhesion. Many studies have been carried out extensively in *Candida albicans*. (25) Biofilms are defined as a ubiquitous in different environments and are formed when microorganisms attach, adhere and accumulate onto surfaces, in which the latter is resistant and can protect from antibiotic treatment. Adhesion of *C. albicans* cells to the surfaces is the first step to stimulate transition, and initiate extracellular matrix, which is organized as a robust structure.

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(26) This is controlled via network of transcription factors of over 1000 genes and that incorporate the expression of adhesins, cellular morphogenesis. (27) (28) Biofilm formation is influenced by different Candida species involved, by distinct patterns of morphogenesis, by environmental agents, and by the type and quality of contact surfaces. In general, cells a biofilm is a cooperating community of adherent that are attached to surfaces and develop by producing extracellular polymers that supply a structural matrix which may assist adhesion. (29) (30) (31)
C. albicans biofilms have four distinct developmental phases (31):

(i) Spherical yeast cells (early-phase) which promote adherance to the surfaces.
(ii) The intermediate phase, where the basal layer of the matrix with proliferating cells is formed by yeast cells switching to a filamentous form.
(iii) The maturation phase with increased anchoring of fungal cells, growth of hyphae concomitant with the production of extracellular matrix material, arranged to produce a three-dimensional architecture.
(iv) The dense network of cells (yeasts, pseudohyphae and hyphae) can slowly disseminate yeast cells from the matrix to seed new sites. (26)

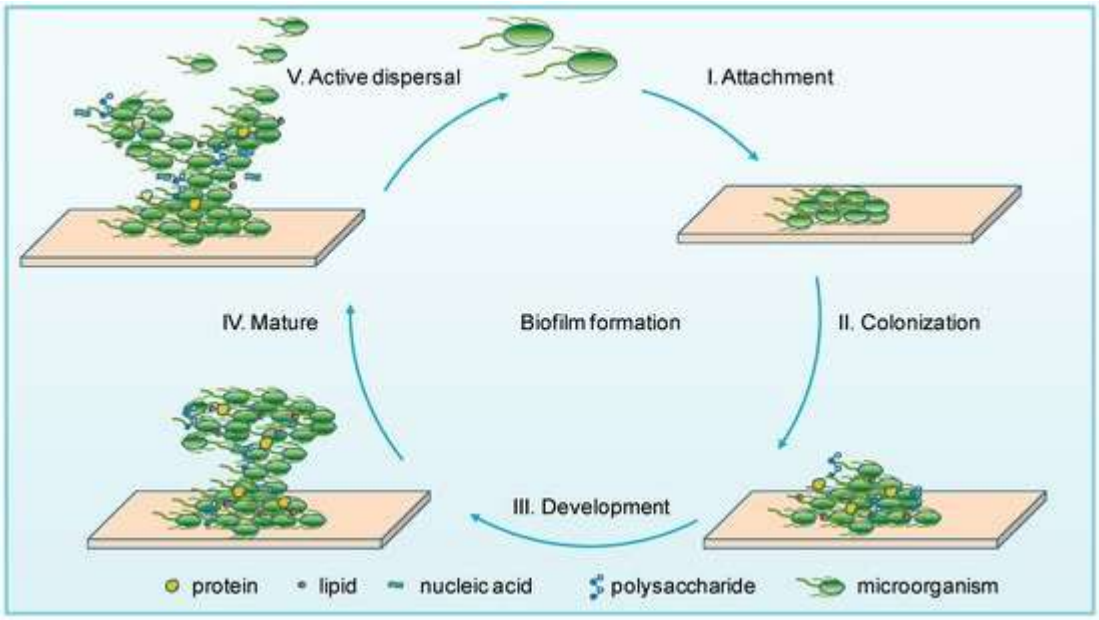

Figure 4. Diagram of microbial biofilm formation. Biofilm formation consists of distinct stages: Attachment, Colonization, Development, Mature and Active dispersal.

Conclusion

The onset of fungal infection depends on various interactions: between different Candida species, and pathogen-host interactions.
The virulence factors are not a fixed property of a microorganism, because the environment can trigger and regulate the expression of virulence genes.
There are two distinct mechanisms of invasion; fungal-induced endocytosis and active penetration, which resulted in candidiasis. The current review provides comprehensive information on candida and its virulence factor, which may induce strategies for colonization and causing pathogenicity.

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الكانديدا و داء المبيضات – إستعراض عوامل الضراوة

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الخلاصة

إزداد حدوث الإصابات بداء المبيضات خلال العقود القليلة الماضية على الرغم من ان المبيضات تعتبر من أكثر أنواع الكائنات الحية شيوعا والتي تسبب الالتهابات الفطرية المكتسبة . يعد جنس *Candida albicans* أحد مسببات الأمراض الفطرية الانتهازية. تتواجد الخميرة بصوره متعايشة في الأفراد الأصحاء ، ويمكن أن تتواجد في جسم الإنسان بشكل غير ضار. ومع ذلك، فان الأفراد الذين يعانون من ضعف المناعة ، يمكن ان يعانوا من إصابات فطريه من خلال قابيله الفطر على غزو الأنسجة ، مما ينتج عنه التهابات سطحية. اما بالنسبة للحالات الشديدة فأنها تؤدي الى إصابات جهازيه مهددة للحياة. تؤدي الأمراض الفطرية إلى معدلات إمراضيه عالية جدًا بالإضافة إلى وفيات تصل إلى 60٪ للأشخاص شديدي التأثر بالعدوى الميكروبيولوجيه. سيركز هذا المقال على عامل الضراوة لـجنس *C. albicans* بما في ذلك (الالتصاق، الغزو، الانزيمات المحللة للكانديدا، التحول المظهري وتكوين الأغشية الحيوية).

الكلمات المفتاحية: *Candida albicans* ، عوامل الضراوة ، داء المبيضات .