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Review of Virulence Factors in Candida

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ABSTRACT

Candida albicans is a prevalent commensal fungus that inhabits various anatomical regions, including the oropharyngeal cavity, gastrointestinal and vaginal tract, as well as the skin of persons in good condition. C. albicans is present in the normal flora of the microbiota in around 50% of the population. The clinical presentations of Candida species encompass a spectrum of symptoms, spanning from localized. The spectrum of mucocutaneous issues ranges from superficial to invasive disorders that impact many organ systems and present a substantial threat to human life. Disruptions in the normal homeostasis of Candida can be attributed to a range of reasons, encompassing systemic and local factors as well as genetic and environmental influences.

These disruptions ultimately lead to a shift from a state of normal flora to the development of Infections caused by pathogens and opportunistic agents. The initiation and advancement of infection are regulated by the virulence characteristics of Candida, which play a role in the emergence of candidiasis. Oral candidiasis presents with a wide range of symptoms, which can be classified into major and minor types. The gastrointestinal tract is the main reservoir for Candida albicans in the human body. Infection occurs due to an imbalance in the local microbiota, impaired immune function, and damage to the intestinal mucosal barrier. Candidaemia, a term used to describe invasive infections caused by candida, is associated with the presence of Candida albicans in the bloodstream. The mutual relationship remains intact by maintaining a balance between the host immune system and C. albicans virulence factors. This study investigates the virulence traits exhibited by Candida albicans. These components have a significant impact on the development of disorders.

Keywords- Candida, Virulence factor, Fungal, biofilm, cell adhere.

I. INTRODUCTION

From the time of the ancient Greeks' identification of fungi until the present day, there has been a shift in the perception of the harmful nature of these microbes. It is currently understood that they are often non-pathogenic for individuals with a robust immune system. Nevertheless, under some clinical circumstances, they can potentially serve as a causative element in the development of serious and perhaps fatal infections [**1**]. It is noteworthy to mention that the prevalence of infections resulting from these bacteria has been consistently rising globally, with fatality rates potentially reaching 60-70% for some patient populations [**1**,**2**,**3**]. Fungal infections encompass both epidemiological and socioeconomic dimensions. Candidosis comprises a diverse array of infections that impact the skin, mucosal linings, and deep-seated organs. These disorders are predominantly attributed to opportunistic pathogens that are classified within the Candida genus[**3**]. One pathological illness that can affect multiple organs is invasive candidosis. Regarding its ability to invade, its pathogenicity, and its susceptibility to antifungal medications, each species of Candida exhibits unique characteristics.[**4**]. Invasive candidosis is a pathological condition that has the ability to impact various organs. Every individual Candida species demonstrates distinct traits in relation to its

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invasive capacity, pathogenicity, and susceptibility to antifungal agents [**5**].

The geographical distribution of Candida species exhibits significant variations, particularly among different hospital sites. The location and frequency of Candida spp are influenced by the patient's underlying illness and prior antifungal medication. [**6**].

Candida albicans is the major pathogen responsible for invasive candidiasis worldwide. There has been an increasing incidence of infections caused by non-albicans Candida species (NACs) in recent years. The negative-acting candidas (NACs) described above include Candida glabrata, Candida parapsilosis, Candida tropicalis, Candida krusei, and Candida auris, among others [7]. In northern European countries and the United States, the dominant species is C. glabrata. On the other hand, India, Pakistan, Latin America and Mediterranean countries have higher frequencies of C. parapsilosis and/or C. tropicalis infections. Like other microbes, Candida species have evolved several effective techniques to increase their ability to cause disease. The primary factor influencing the ability of Candida to cause disease is its inherent ability to attach to the inanimate surfaces of medical devices and synthetic materials, as well as to the mucosal epithelium of the host. The acquisition of this talent is crucial for the formation of biofilms, thereby leading to detrimental effects on the host organism[8,9].

It has been shown by researchers that the capacity of Candida species to establish colonies on mucosal surfaces or inert materials exhibits variability [10].

II. THE VIRULENCE OF CANDIDA SPP.

The virulence of a microbial species is determined by the result of interactions between the germ and the host, rather than being an inherent characteristic of the bacteria. In contrast to primary pathogens, which thrive in the absence of host injury, opportunistic/facultative pathogens, such as Candida spp., primarily induce disease in hosts that are susceptible to infection. The environmental factors exert a significant influence on the tactics employed to counteract the hosts' innate defense mechanisms. Virulence is a dynamic characteristic that can be augmented, diminished, and potentially reinstated under different conditions. [**11**]. Candida albicans has the ability to transform from commensal to pathogenic and aided by its ability to adhesion, biofilm growth, hydrolytic enzyme release, morphological change and metabolic adaptability. In addition, rapidly adapt to the host environment and infect people with predisposing factors such as antibiotic treatment, malignancy, or weakened immune systems.

Candida albicans attempts to evade the immune response and survive in diverse host conditions, while the host barrier and immune cells attempt to prevent or reduce infection. Commensal organisms can cause disease when interactions between host and pathogen are imbalanced. Host innate immunity is vital to combat fungal infections. Through redox mechanisms or extracellular traps, neutrophils can prevent Candida yeast from becoming filaments. Monocytes, macrophages, the complement system, Toll-like receptors, and lectins generate pro-inflammatory cytokines and chemokines, which influence the host immune response. These components cooperate to determine fungal molecular patterns such as nucleic acids, mannans, and beta-glucan [**12**]. Candida spp. have evolved evasion tactics as a means to elude the immune system. The immune system possesses the ability to readily identify a specific polysaccharide known as β-glucan within the cell wall. However, β-glucan is concealed within The outer mannoprotein layer of the cell wall facilitates the evasion of the host's identifying systems by the cell wall structure.. [**13**].

2.1. Adherence and Invasion of the Host Cells

The first step for infection by Candida albicans is attachment that aided by several factors including, adhesion proteins (which is specific proteins found on surface of Candida spp), immobilized ligands(cadherine, and integrins) or indirectly by other micoorganism . Follow attachment, it is necessary for the cells to enter the tissue. The pathogenicity of the condition is mostly ascribed to the invasion and subsequent destruction of the epithelial tissue[**14**].

The process can take place by either induced active penetration or endocytosis, depending on the specific characteristics of the host cell. In the case of C. albicans, the invasion of oral cells necessitates the utilization of both endocytosis and active penetration mechanisms. On the other hand, enterocytes can be invaded exclusively by actively penetrating them [**15**].

The process of attachment of yeasts to the surface of host cells occurs through adhesion proteins such as als 1-7, hwp[16], eap1[17] and pgal[18]. The family of ALS which are found in the candida albicans, is associated with invasion, adhesion, and iron acquisition. The ALS gene family is responsible for 8 cell wall proteins as ALS1-7 and ALS-9. These proteins act as facilitator for adhesion to host epithelial cells. The strains of opportunistic yeast express genes responsible for coding adhesion proteins, transporters, and oligopeptides[19]. In addition, virulent proteins carry genes related to filamentous proliferation, biofilm development and cell wall architecture. The interactions between non livings substances and ALS proteins affected by hydrophobicity play a critical role in the production of biofilm, such as those in prosthetic devices[20].

A surface protein (ALS3), found in the hypha of Candida albicans facilitates attachment of yeast cells with different types of cells, such as epithelial cells, endothelial cells, and extracellular matrix proteins. ALS3

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binds with cell receptors such as E-cadherin and N-cadherin cause stimulates the phagocytosis of microorganisms. In addition, ALS3 allows for Candida albicans to benefit from ferritin as a source of iron by binding with ferritin that is found in host cells[21]. Finally ALS3 also penetrates the host cell, there for it consider a target for vaccination[20,21].

In contrast, Eap1 is a protein found in the cell wall that binds with glycosylphosphatidylinositol and is expressed by the EAP1gene. Eap1was noticed to have an effect on attachment and biofilm formation in vivo and in vitro[17].

Pga1 proteins composed of 133 amino acids bind with GPI. Its functions are adhesion, biofilm production, and maintaining cell integrity[18]. C. glabrata depend on Epa proteins and Epa-like proteins to attach to host cells.These adhesins are produced by EPA, a gene family located in the subtelomeric region. Epa1 is a pivotal factor in the process of adhering to epithelial cells, and it exhibits a notable degree of heterogeneity. As the diversity of this adhesin rises, the likelihood of hypervirulent strains also increases. [**21**]. Epa6 and Epa7 play a crucial role in the pathogenesis of Urinary tract infections (UTIs). The increase in EPA genes depends on the presence of nicotinic acid (NA) in the surrounding environment.. [**22**].

C. parapsilosis contains a total of five ALS genes and six genes for Pga30, a protein predicted to bind to the cell membrane by glycophosphatidylinositol. These genes are likely involved in the adhesion process. However, more work is needed to confirm the function of NCAS. [**23**]. Approximately 1-10% of the C. parapsilosis isolates that were identified using standard biochemical assays have been confirmed to be either C. metapsilosis or C. orthopsilosis. The adhesion properties of C. orthopsilosis and C. parapsilosis exhibit similarities[**24**], C. metapsilosis is less virulent [**25**].

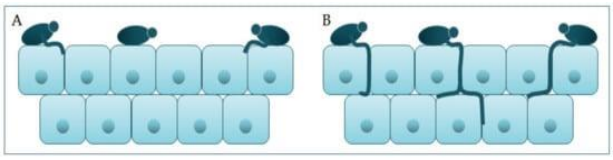

Figure 1. Schematic presentation of (A) adherence and colonization, and (B) penetration and invasion of *C. albicans*.

2.2 Adaptability to Changing Environmental Conditions, Dimorphism and Phenotypic Switching:

Candida albicans, in contrast to other Candida species, able display different morphological forms, this phenomena are called dimorphism, which indicates that C. albicans may exist in the form of blastoconidia (terms used interchangeably), hyphae and blastospores. There are four form of polymorphism growth including, true hyphae, pseudohtphae, germ tubes, and blastospores[**26,27,28**]. *C. dubliniensis* has been verified as a really polymorphic fungus[**29**,**30**,**31**]. Simultaneously, the potential for C. parapsilosis and C. tropicalis to generate pseudo-hyphae is elucidated[**32**]. C. glabrata is an example of a Candida species that does not possess this capability. It exclusively grows in the form of exceedingly small blastospores[33]. Candida spp have the ability to adapted to the surrounding environment and it is closely related to dimorphism. some strains have the ability to adapted to change in oxygen availability, PH, temperature, and deficiency of nutrition. The phenotypic transformation is reversible and can transform the hypha into blastula.[**34**,**35**]. Several studies indicate that the morphology of yeast or blastophores is associated with the colonization and spread of candida within living host cell. Hyphae are known for their invasive nature and are able to attach strongly to the host tissue , secrete hydrolytic enzymes, and cause damage to tissues[**36**,**37,38**]. Furthermore, filaments possess the capacity to endure in macrophages and exhibit diminished vulnerability or resistance to antifungal drugs that target Y forms, unlike blastospores. [,35,**39**]. This demonstrates the significance of phenotypic switching variation as a virulent factor that plays a crucial function in infection. The concept positing that the virulence and infection growth of Candida spp. necessitate the presence of hyphae and subsequent phenotypic flipping is being called into doubt. [**34**,**38**,] Extensive genetic research conducted in the last twenty years has yielded a substantial amount of highly valuable data regarding the control and origins of morphological and phenotypic alterations in Candida fungi. However, the scientists acknowledge that there is still more knowledge to be uncovered. The observed phenomena encompass the involvement of transcription factors that facilitate hyphae growth, such as, Cph1, Efg1, Cph2, Czf1, Tec1, Ndt8, and Rim101, as well as negative regulators specific to hyphae, such as Tup1, Nrg1, and Rfg1. Additionally, these factors are also involved in the entirety of signal transduction pathways. In addition, they oversee variables and processes associated with other Candida virulence factors. Therefore, it is challenging to determine if mutant strains of C. albicans lacking the genes Efg1 and Cph1, which are incapable of producing hyphae, exhibit diminished virulence as a result of the absence of a hyphae structure. Cell wall proteins, such as adhesins and sap, may exhibit reduced gene expression due to the influence of the Efg1 and Cph1 genes and their activation pathways [27,**34**,**40**,]

2.3 cell wall:

The cell wall assumes a pivotal and significant function, as it serves as the initial interface with the host cells and harbors crucial antigenic determinants for the fungus. This particular location is accountable for the release of virulence factors as well as the release of antibodies and fungal antigens. Consequently, the organism will progress into a pathogenic condition, or the exacerbation of a resistance response by the host. [41]

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2.4 : Extracellular hydrolytic enzymes

Fungi utilize extracellular hydrolytic enzymes to burst and penetrate host tissues. [42]. Hence, it is anticipated that they possess the potential to serve as virulence factors. Lipases, phospholipases, and proteinases are among the significant enzymes. Multiple investigations have documented a decrease in the dangerousness of Candida spp. as a result of the lack or decreased presence of these hydrolytic enzymes. These enzymes facilitate the morphological changes, colonization, and penetration of host tissues in Candida cells. [42–43]. Phospholipases play a crucial role in promoting the invasion of Candida cells into host tissues through the hydrolysis of ester bonds present in glycophospholipids. The findings of Ibrahim et al.'s study indicate that invasive strains of Candida albicans exhibit a greater production of phospholipases in comparison to noninvasive strains. [44]. C. albicans has four distinct forms of phospholipases, namely phospholipase A, B, C, and D. These categorizations are based on the enzyme's capacity to cleave a certain ester bond. [43]. Numerous studies have documented that the ability of Candida cells to invade epithelial tissues is enhanced by an increased synthesis of phospholipases. [45–46].

The secretion of aspartyl proteinases (SAPs) is of paramount importance in the pathogenicity of Candida. During the infective process, a group of ten SAPs (Sap proteins) perform various specific activities. Hemoglobin is metabolized by SAPs in order to obtain nutrients for Candida cells. The host cell membrane is disrupted through the hydrolysis of various tissue proteins, including albumin, collagen, cystatin A, keratin, laminin, and fibronectin, in order to promote adhesion and invasion of the host tissue. SAP causes degradation of immune system cell and chemical substance for host cells such as IL-1B, IgA, mucin, and lactoferin, in order to avoid antimicrobial attack. ALS3 production is linked with other factors such as adhesion, and phenotyping that contribute to increase pathogenicity[47,48].

2.5: Biofilm formation :

Biofilm production is affected by a range of variables, such as the interaction of the host cell with yeast . Candida albicans is able to produce biofilms with a period ranging from 24-72 hours. The process is complex and consists of several stages, in the first stage, yeast binds with living or non-living surfaces. Biofilm production continues with cellular growth and adherent cell filamentation. After then, biofilm matures. The final stage of biofilm production is dispersion, when yeast cells leave the biofilm and enter the environment. Biofilm formation varies per Candida species. Candida yeasts' ability to grow and produce biofilms is also regulated by host homeostasis, variations (such as mucosal pH or nutrition), and immune system health [49]. In the adhesion phase, individual cells attach to a suitable surface, grow into small groups called microcolonies, and create a base layer. The in vitro adhesion process typically requires roughly 11 hours. [49,50]. Every species of Candida possesses distinct characteristics. Candida albicans exhibits a higher degree of adherence to the epithelial cells found in the gastrointestinal tract, urogenital tract, and endothelium of blood vessels compared to Candida glabrata. C. glabrata has enhanced platelet adhesion, facilitating efficient distribution within the bloodstream, particularly in cases of widespread infection. [51]. *C. tropicalis* exhibits higher virulence in individuals with low neutropenia, typically resulting in the spread of the virus to peripheral organs through the bloodstream. *Candida tropicalis* is a common organism that often inhabits the upper respiratory system and creates biofilms on the tubes of the trachea. [52,53]. *C. parapsilosis* has the capability to develop resilient biofilms on central venous catheters, posing a significant risk to undernourished infants and neonates with low birth weight. [54,55]. Adherence is facilitated by adhesins, which are glycoproteins situated on the cell wall's surface. Various genes encode the adhesins, which are expressed throughout distinct stages of yeast cell growth and development. Fungal adhesins facilitate cellular contacts, such as flocculation and filamentation, as well as interactions between cells and inert surfaces like agar and plastic material, and hosts tissues. [51,56,57]. Candida adhesion is determined by multiple gene families. Genes and their regulation vary greatly, depending on the yeast species. Multiple layers of variety exist, including strain-specific and allele-specific gene size, gene regulation, and gene absence in certain isolates [58,59,60,]. The EPA (epithelial adhesin) gene family encodes a primary set of adhesins in C. glabrata. [61]. Additional variables can also influence the sticky characteristic. One of the factors contributing to cell adherence to surfaces is cell surface hydrophobicity, which exhibits variability across different species. C. parapsilosis and C. tropicalis exhibited the strongest correlation between hydrophobicity and improved adhesion. [62]. The cell wall of C. krusei exhibited a greater degree of hydrophobicity when compared to C. albicans. Furthermore, a positive association between hydrophobicity and adherence to HeLa cells was established. [63]. The principal point of interaction between the pathogen and the host surface occurs within the fibrillar layer of the cell wall. The composition mostly comprises glycoproteins, with the bulk falling under the category of mannoproteins. The hydrophobic nature of the cell wall is mostly attributed to the glycosylated mannoproteins present in its outer layer, particularly the acid-labile fractions of phosphomannoproteins. [63,64]. Morphological alterations occur during the process of biofilm multiplication, which is considered the intermediate phase. Cell proliferation and cellular filamentation take place. The formation of a biofilm relies on the yeast's ability to produce extracellular polymeric substances

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(EPSs), which consist of polysaccharides, glucose, hexosamine, lipids, proteins, phosphoric acid, uronic acid, and other chemicals. The duration of the proliferative phase is approximately 12 to 30 hours. Microcolonies appear on the newly formed monolayer, and are then followed by the formation of macrocolonies consisting of yeast cells, germ tubes, and young hyphae. The maturation phase normally ends after approximately 72 hours after biofilm development begins. Maturation leads to the formation of an intricate network consisting of multiple layers of polymorphic cells. These cells consists of hyphal cells, which are cylinder shaped and arranged as chains, pseudohyphal cells which are ellipsoidal cells bind with each other, and round yeast cells surrounded by an extracellular matrix. During cellular division, many pores and channels of water are created that enhance the active transfer of molecules between host cells and cells in biofilms[65]. The extracellular matrix consists of extrapolymer substances consisting of dense packets from filamentous and yeast cells. The creation of EPS depends on carbon, which is essential for maintains stability of biofilms, in addition protect against phagocytosis and antibiotics. The main component of EPS is polysaccharide, which is 40%. After biofilm formation, dispersal phase occurred, during this phase, daughter cells dispersed from biofilms to surrounding surface[66, 67]. The formation of biofilms by candida albicans differ in vitro than vivo, an example, biofilm formed after 24 hours after the insertion of a tiny catheter in rats, while in vitro biofilms forms after 24 -72 hours[68,69].

In regarding to Cglabrata, the biofilms formation occur rapidely in vitro than vivo[70]. The biofilm formation affected by several factors such as types of yeasts, the surface of host cell, PH, O2 concentration, in addition the formation of biofilms in candida albicans affected by mineral ions concentration in the surrounding cells[71, 72]. The study shown that an augmented flow rate of the medium has a notable and favorable impact on the matrix formation process. [66]. Among the various Candida species that hold medical significance, Candida albicans is widely recognized as the most prominent and influential generator of biofilms. Candida albicans exhibits polymorphism, displaying the capacity to generate genuine hyphae as well as pseudohyphae, which are more commonly observed (Figure 2). The hyphae in question originate from yeast cells or emerge as extensions of pre-existing hyphae. Pseudohyphae are generated through the process of budding with yeast cells or hyphae. The progeny of pseudohyphae remains connected to the parent cell and undergoes elongation, leading to the formation of filaments that exhibit constrictions at cell-cell junctions. However, these pseudohyphae lack the internal dividing wall, known as the septum, which is characteristic of true hyphae[73]. The humanmicroflora, consisting of bacteria, fungi, and viruses, invariably show that they produce polymicrobial biofilms that are even more complex to manage than monomicrobial ones[74]

Figure 2. *Candida* cells, pseudohyphae, and true hyphae.

III. CONCLUSIONS

Understanding the reasons and mechanisms underlying the pathogenicity of Candida albicans is of utmost significance due to its extensive spectrum, encompassing variations in morphology, formation of biofilms, thigmotropism, production. The process entails the presence of adhesion proteins and the secretion of extracellular hydrolytic enzymes. Candida albicans has the ability to provoke infections that can vary in severity from superficial to systemic, and in some cases, can be life-threatening.

Furthermore, it is important to have an understanding of the basic elements that make a person vulnerable to candidiasis, as well as the factors that contribute to its severity. Predisposing factors include neutropenia, immunosuppression, diabetes, and advanced age, as well as patient care-related factors such as prolonged antimicrobial drug administration, prolonged hospitalization, catheter use, and surgical procedures. As the understanding of these many aspects expands, the potential for prevention also grows, as efforts are made to mitigate the incidence of infections caused by C. albicans. Consequently, novel prospects arise for the development of diagnostic and therapeutic interventions.

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