# Chapter 17
# Adaptation of *Candida albicans* for Growth Within the Host

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**Abstract** One of the most important attributes of microorganisms is their ability to biologically adapt to every environment on earth. Microorganisms possess sophisticated signaling systems that enable them to sense and respond to environmental changes and challenges. Typically, this response results in morphological, physiological and even genetic differentiations. The genetic information associated with a microbe is capable of alterations which are sometimes reversible, and disappearing when the particular pressure is lifted. Other alterations are maintained and can even be passed on to succeeding generations of bacteria. This fact may well indicate that the structure can be modified to maintain function under environmental stress. *Candida albicans*, commonly found as a component of the normal flora of humans, residing in the gastrointestinal tract, in the genitourinary tract and on the skin, is the most common opportunistic human pathogen. The yeast is a harmless commensal in most healthy people, but it causes superficial as well as life-threatening systemic infections in immunocompromised patients. The ability of *C. albicans* to be virulent depends completely on its yeast-to-hyphae switch where the organism changes from a unicellular yeast form to a multicellular hyphal form. This switch may likely be induced by environmental conditions like temperature, pH and nutrients. This chapter presents the regulatory adaptation mechanisms that make *C. albicans* the most successful fungal pathogen of humans.

**Keywords** *Candida albicans* • Adaptation mechanisms • Environmental stress

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## 1 Introduction

The ability of microorganisms to sense and adapt to changes in the external environment is essential for their survival. This adaptation to environmental conditions is particularly important for the survival of fungal species growing with a close association with host organisms, such as pathogens, symbionts or commensals (Vylkova et al. 2011). Accordingly, the yeast *Candida albicans* is both a harmless commensal and an aggressive pathogen (Wächtler et al. 2011). Since *C. albicans* lacks any typical environmental habitat, their cells generally adapt to diverse environmental conditions, each with its own specific set of environmental pressures, with ease within very short time periods. *Candida albicans* has even adapted to grow in association with the human host whereby the human immune system has allowed it.

The fungus is found as a commensal in most healthy individuals. As commensals, *Candida* species are harmless and the population is colonized with *C. albicans* without any signs of diseases. However, if the balance of the normal flora is disrupted or the immune defenses are compromised, *C. albicans* frequently outgrows the microbial flora and causes symptoms of diseases (Mavor et al. 2005). Therefore, *C. albicans* is able to switch between being a commensal and a pathogen (Rupp 2007; Schulze and Sonnenborn 2009). However, the cause of transition from a harmless commensal to an aggressive pathogen (Wächtler et al. 2011), and the stable maintenance between commensalism and pathogenicity is still not known (Sohn et al. 2006; Rupp 2007). Nevertheless, by using the host as an environment, *C. albicans* has got to not only develop mechanisms to colonize and invade into the host, but also need to possess particular attributes to persist in the host in large numbers without causing any damages. Undoubtedly, both host and microbial factors are required to maintain the balance from commensalisms to host damage and *vice versa* (Rupp 2007).

Thus, this chapter focuses on the recently identified systems for adaptation of *C. albicans* during colonization and infection of their human host and the role of these systems in the fungal survival and virulence.

## 2 Epidemiology

Humans harbor *C. albicans* during or shortly after birth wherein it almost immediately colonizes the newborn and becomes a commensal (Khan and Gyanchandani 1998; Calderone and Fonzi 2001; Khan et al. 2010). The growth of the yeast is kept under control by the infant's immune system and thus produces no signs of diseases. Accordingly, it is presumed that by 6 months of age, 90% of all babies are colonized by *C. albicans*. By adulthood, almost all humans become involved in a life-long relationship and play host to *C. albicans*. Since *C. albicans* is part of the normal flora, it is normal for all humans to have controlled quantities of the organism.

*Candida albicans* being the most common commensal fungi in healthy individuals (Pinto et al. 2008), rarely causes diseases in immunocompetent hosts (Khan et al. 2010).

The fungi are normally found as commensals in the human oral cavity, gastrointestinal tract, genitourinary tract, diseased skin and mucosal membranes (Baron et al. 1994; Forche et al. 2011). As commensals, *C. albicans* competes with other microbes for nutrition in different body sites and adapts to different host conditions like temperature, pH and nutrients within the host (Calderone 2002). Moreover, the physical barriers such as epithelial layers and a functional immune system maintain the commensal phase of *C. albicans* in the host (Wächtler et al. 2011). Therefore, commensally growing *C. albicans* are controlled by the normal microbial flora and the immune response of the host (Mavor et al. 2005).

In order to survive in a niche, a fungus has to adapt to constantly changing parameters wherein *C. albicans* has been found to respond to these environmental changes by inducing transcriptional and translational changes for adaptation in the new environmental conditions (Khan et al. 2010). Success of survival also depends on rapid adaptations to changing micro-environments and likewise, as *C. albicans* enters the human host, their lifestyle changes from harmless commensals to opportunistic pathogens. Opportunistic pathogens, when given the opportunity, will attempt to colonize all bodily tissues. Thereby, under conditions of weakened immunity (people with Acquired Immunodeficiency Syndrome (AIDS), leukemia or cancer) or imbalance in the commensal flora, *C. albicans* becomes an opportunistic pathogen and causes diseases ranging from mild superficial infections (such as oral thrush and vaginitis) to severe, life-threatening bloodstream infections (such as disseminated candidiasis) (Forche et al. 2011). *Candida albicans* takes the advantage of certain predisposing events to cause diseases (Baron et al. 1994). These different candidal infections therefore involve adaptation of *C. albicans* to different host environmental niches and growth conditions (Forche et al. 2011).

## 3 Mycology

*Candida albicans* is an asexual oval-shaped diploid fungus of the Ascomycetes. A number of such fungi are causal agents of opportunistic infections in humans (Baron et al. 1994). Some species show phenotypic switching, a variant colony morphology (Khan et al. 2010). They grow both as yeast and filamentous cells on various mucosal surfaces of the body, including the oral cavity, gastrointestinal tract and vaginal mucosa. The predominant asexual reproductive unit of the yeast is a blastoconidium (Baron et al. 1994).

### *3.1 Candida albicans Strain Variation*

*Candida albicans* infection in the majority of cases is a patient's own commensal flora. Evidence suggests many individuals harbor a mixture of strain types of minor variants, typically differing in levels of genetic heterozygosity (Odds 2010). As such,

more than one distinctly different *C. albicans* strain type may be found in a small proportion of individuals in a single sample from a single anatomical site (Jacobsen et al. 2008), and in longitudinal samples from the same site or different anatomical sites (Odds et al. 2006a; Bougnoux et al. 2006). These interstrain differences may indicate strain replacement (Bartie et al. 2001). However, strain replacements are much less common than a single type with minor variations (Odds 2010). This single *C. albicans* strain type with minor variations may suggest microadaptations of *C. albicans* on the host.

## *3.2 Organism Characteristics*

### 3.2.1 General Characteristics

An unusual feature of *C. albicans* is its ability to grow either as an unicellular budding yeast or in filamentous pseudohyphal and hyphal forms (Odds 1988; Sudbery et al. 2004). Pseudohyphae are morphologically distinguishable from the hyphae form whereby the former have constrictions at the sites of septation and are wider than the latter. By contrast, hyphae form long tube-like filaments with completely parallel sides and no constrictions at the sites of septation (Sudbery 2011).

### 3.2.2 Cell Wall Structure

The cell wall is crucial for colonization and infection since it defines the interface between host and pathogen. It is one of the major structures, comprising 15–25% of the dry weight of the cell of which approximately 80–90% of the cell wall of *C. albicans* consists of carbohydrates. Three basic constituents representing the major components of the cell wall are complex polymers of glucose (β-1,3- and β-1,6-glucan), chitin (N-acetylglucosamine) and polymers of mannan (mannoproteins). The glucans make up 50–60% of the total mass of the cell wall, whereas chitin constitutes 0.6–2%, and mannan moiety of mannoproteins represents 30–40% of the cell wall polysaccharides in *C. albicans*. The rigid structure of complex polymers of glucose and chitin surrounds the cell like a shield, protects it from environmental stresses like osmotic pressure and defines the shape and physical strength of the fungal cell (Sohn et al. 2006). In addition, cell walls contain 6–25% proteins and minor amounts of 1–7% lipid. However, the protein composition of the cell wall varies greatly according to the different cell morphologies like the yeast, pseudohyphal and hyphal form. Also, the expression pattern of cell wall proteins in hyphae varies with the different stimuli induced. Accordingly, it has been shown that cell surface proteins determine the adhesion (Rupp 2007), colonization and infection of host cells and any alterations in the protein composition of the cell wall may result in reduced virulence of *C. albicans* (Sohn et al. 2006). This shows that host and pathogen interact and this interaction is controlled by several signaling systems of *C. albicans*.

## 4 *Candida albicans* Infections

Fungal infections also commonly occur in the healthy population. Healthy persons generally encounter superficial infections but immunocompromised patients face invasive infections (Khan et al. 2010). As such, *C. albicans* has been reported to be the fourth most common cause of nosocomial infections in the USA and elsewhere in the world (Wenzel 1995). The ability of *C. albicans* to adapt and survive at different anatomic sites of the human host has also made them more harmful than other commensals of the human body (Khan et al. 2010). As commensals of the normal flora, *C. albicans* causes superficial infections and epithelial damage when it overgrows the microbial flora (Mavor et al. 2005). However, in severe cases, the fungus penetrates through epithelial layers into deeper tissues and may cause life-threatening systemic infections (Wächtler et al. 2011). Infections caused by this pathogen normally include cutaneous lesions, mucous membranes and systemic disseminated diseases.

### *4.1 Cutaneous Lesions*

Superficial *Candida* infections include intertrigo (warm and moist environment like skin folds), diaper rash and nail infections. Commensal *Candida* infections rapidly colonize damaged skin or skin areas with closely opposing surfaces, such as the diaper area in infants and toddlers and abdominal fat folds and groin in older individuals. *Candida albicans* also causes candidal onchomychosis in the nails or the area around the nail and such infections produces lesions that resemble those produced by dermatophytes. Nail infection almost always includes involvement of the area around the nail leading to club-shaped fingers (Baron et al. 1994).

### *4.2 Mucous Membranes*

The ability of *C. albicans* to live as a commensal on mucosal surfaces of healthy individuals often cause superficial infections of mucous membranes and may lead to a condition known as thrush (Baron et al. 1994; Mavor et al. 2005). The mucosal surface of the vagina is a frequent site of *Candida* infection (vulvovaginitis). Approximately 70% of women experience vaginal candidiasis once in a life and 20% suffer from recurrence (Baron et al. 1994; Fidel et al. 1999), however, the reasons for repeated attacks are not known.

### *4.3 Systemic Disseminated Disease*

The *Candida* cells which manage to penetrate into deeper tissues cause severe systemic infections in immunocompromised patients, in children with AIDS and other immune deficiencies, as well as in very low birth weight premature infants. When a person is

severely immunocompromised, *C. albicans* enters the bloodstream and causes infection of the bloodstream which leads to serious problems, especially in the kidneys, heart, lungs, eyes, brain and many other organs. Furthermore, in the severely immunocompromised host, *C. albicans* may also cause life-threatening systemic infections.

## 5 *Candida albicans* Pathogenesis and Virulence Factors

Although *C. albicans* is a commensal, the organism is also an important opportunistic pathogen (Rosenbach et al. 2010). Like other fungal pathogens, *C. albicans* regulates the expression of certain genes as virulence factors to produce disease. Some of virulence factors include the ability to recognize and adhere to host tissues, to respond rapidly to changes in the external environment and to secrete hydrolases (Khan et al. 2010). Some of the commonly studied virulence factors in *C. albicans* are briefly described here.

### *5.1 Genetics*

*Candida albicans* is a diploid organism but is unable to undergo meiotic division to a haploid phase. However, it has developed unusual mechanisms for maintenance of genetic diversity in the absence of a complete sexual cycle. These include chromosomal polymorphisms, with partial ploidy changes for some chromosomes, mitotic recombination events, and gains and losses of heterozygosity (Odds 2010). Amongst these, loss of heterozygosity (LOH) has been widely observed among closely related *C. albicans* isolates undergoing microadaptation (Shepherd et al. 1985; Tavanti et al. 2004; Odds et al. 2006b). Forche et al. (2011) measured the rates of LOH and the types of LOH events that appeared in the presence and absence of physiologically relevant stresses and found that stress causes a significant increase in the rates of LOH. This increase in the rates of LOH is proportional to the degree of stress and is expected to facilitate the adaptation of *C. albicans* to changing environments within the host.

### *5.2 Adherence*

The first step in infection is interaction with the host cells by adhesion. *Candida albicans* expresses various adhesins, which bind to extracellular matrix proteins of mucosal or endothelial cells. The well-known adhesins include members of the agglutin-like (Als) family of adhesins, hyphal wall protein 1 (Hwp1), which forms covalent bonds with the host cell through the action of host cell transglutaminases (Staab et al. 1999) and elF4E-associated protein 1 (Eap1), which is a hypha-specific protein that confers adhesive properties to *Saccharomyces cerevisiae* cells when

heterologously expressed (Li and Palecek 2008). Most *Candida albicans* adhesins are glycoproteins (Mavor et al. 2005). Adhesins promote the binding of the organism to host cells via hydrophobic interactions and the variability of adhesins gives diversity to host cells invasion. The adhesin genes are also differentially expressed according to the environmental conditions.

## *5.3 Filament Formation*

Morphogenesis in *C. albicans* is defined as a switch from unicellular yeast form to filamentous form (pseudohyphae or hyphae) (Khan et al. 2010). As such, many human fungal pathogens are morphogenetic. Accordingly, Calderone and Fonzi (2001) found filamentation to increase the ability of *C. albicans* to cause infection and associated the yeast form with asymptomatic carriage and the hyphae form with active infection. Similarly, Mavor et al. (2005) suggested that yeast cells are better suited for dissemination while hyphae are important for tissue and organ invasion. Furthermore, strains of *C. albicans* that are unable to switch between yeast and hyphal growth forms were avirulent (Sohn et al. 2006). All these suggested that the yeast and hyphal growth forms play different roles in causing infections (Mavor et al. 2005) and therefore, each morphological form has a varying virulence factor which differs with particular environments.

## *5.4 Proteases*

Secreted aspartly proteinases (Saps) from *Candida* have been reported to hydrolyze many proteins. To date, ten proteins have been recognized as Sap family (Saps 1–10) and found to be responsible for tissue invasion (Khan et al. 2010). Phospholipases are enzymes that hydrolyze ester linkages of glycophospholipids and in *C. albicans*, four types of phospholipases have been found. Phospholipase activity was observed in 99.4% of the strains of *C. albicans* tested (Pinto et al. 2008) and that results were similar to those obtained by Kantarcioğlu and Yücel (2002) who described 94% of the strains of *C. albicans* as phospholipase producers. Accordingly, phospholipases and Saps secretion in *Candida albicans* has been considered as relevant virulence factors (Pinto et al. 2008).

## *5.5 Phenotypic Switching*

Phenotypic switching also plays a role in altering the yeast's adherence properties, antigen expression and tissue affinity (Mavor et al. 2005).This phenotypic switching provides cells with the flexibility for adaptation of the organism to the hostile conditions

imposed by the host and aids survival in different microenvironments. This switching is reversible, occurs spontaneously in stress, and results in changes in cell surface behaviour, colony appearance, and metabolic, biochemical and molecular attributes to become more virulent and effective during infection (Odds et al. 2006b). Strains isolated from vaginitis or systemically infected patients showed higher frequencies of switching, indicating a strong role for the switching phenomenon in establishing diseases (Kvaal et al. 1999).

## 6 Adaptation of *Candida albicans* to the Host

For being a successful human commensal and pathogen, *C. albicans* has developed host adaptation mechanisms on various levels. The regulated expression of virulence and other genes in response to environmental signals allows effective adaptation to new host niches during the course of an infection. When fungi invade a mammalian host their lifestyle converts from saprophytic to parasitic. As saprophytes, fungi survive in an environment with a moderate ambient temperature and pH, defined sources for crucial nutrients such as carbon and metal ions, and atmospheric concentrations of gases like carbon dioxide and oxygen. By invading a human host, these environmental factors undergo a sudden and drastic change where ambient temperature is suddenly replaced with the restrictively high temperature of the human body. Ambient pH is replaced with acidic mucosal surfaces or neutral blood and tissues. Known sources of carbon and metal ions are missing in an environment where essential nutrients are sequestered from microbes to support host survival. Carbon dioxide and oxygen concentrations are reversed in host tissues, leaving *C. albicans* to adapt to hypoxia and high levels of carbon dioxide. Herein, we concentrate on recently studied adaptation mechanisms to the abiotic stresses that *C. albicans* encounter during colonization and infection of their human hosts and review the functions of these mechanisms in *C. albicans* survival and virulence.

### *6.1 Thermal Adaptation*

Fungal survival at the high temperature of a human host is essential for virulence. Fungi often develop morphogenetic virulence mechanisms, e.g., formation of yeasts, hyphae, and spherules that facilitate their multiplication within the host at higher temperature. Yeast cells of many *Candida* species produce filamentous pseudohyphae and hyphae in tissues (Khan et al. 2010). *C. albicans* alters from commensal yeast to invasive hyphae at this elevated temperature.

The exact mechanisms by which thermal adaptation is regulated in eukaryotic cells have been widely studied, but are still not yet completely understood. However, it was found that when yeast cells are exposed to an acute thermal stress, proteins unfold, the heat shock transcription factor becomes activated by

phosphorylation and this promotes the expression of heat shock genes (Leach et al. 2012). Recently, researchers identified Ryp1, a homolog of the *C. albicans* transcriptional regulator Wor1, as essential regulator for thermal dimorphism in response to elevated temperature. Ryp1 binds its own promoter and might act as an autoregulatory transcriptional regulator in *C. albicans*. Ryp1 mutants grow as hyphae and are unable to induce expression of most yeast phase-specific genes at 37°C (Cooney and Klein 2008).

The heat shock response in *C. albicans* has been of interest for few reasons. First, temperature up-shifts induce morphological changes from the yeast to hyphae and this cellular morphogenesis is a major virulence factor in *C. albicans*. Second, mutations that block heat shock transcription factor (Hsf1) activation in *C. albicans* prevent thermal adaptation and significantly decrease the virulence of *C. albicans*. Third, antifungal drug resistance is abrogated by Hsp90 inhibitors and by elevated temperatures equivalent to those in febrile patients. Fourth, *C. albicans* heat shock proteins are immunogenic, so, directly affecting host-pathogen interactions during infection. Last, autoantibodies against Hsp90 are immunoprotective against *C. albicans* infections (Leach et al. 2012).

To summarize, the thermal adaptation of fungal pathogens is of high importance because it is crucial for virulence, and because heat shock proteins represent targets for novel therapeutic strategies.

## *6.2 pH Adaptation*

The capability of fungal pathogens to cause disease depends on their ability to survive within the human host environment. Generally, ambient pH is replaced with acidic conditions of mucosal surfaces or neutral to slightly alkaline pH of blood and tissues, and the ability of fungi to grow at this pH is crucial for pathogenesis. The Rim101 signal transduction pathway is the primary pH sensing pathway described in the pathogenic fungi, and in *C. albicans*, it is essential for a variety of diseases (Davis 2009). Rim101 is essential for *C. albicans* virulence in models of mucosal invasion and systemic candidiasis (Davis et al. 2000). Rim101 is activated downstream of a signaling cascade involving a plasma membrane complex, an endosomal membrane complex, and the proteasomes

The proteins of the plasma membrane signaling complex undergo pH-dependent activation. PalI/Rim9 is responsible for localization of the pH-sensor PalH/Rim21 to the plasma membrane (Calcagno-Pizarelli et al. 2007). This facilitates PalH-dependent phosphorylation and ubiquitylation of PalF/Rim8. PalF is an arrestin-like protein thought to trigger endocytosis of the plasma membrane complex upon PalH-dependent modification, mediating transduction of the pH signal from the plasma membrane to the endosomal membrane (Herranz et al. 2005). PalH is also required for localization of the endosomal complex protein PalC to the endosomal membrane (Galindo et al. 2007). This occurs through interaction of PalC with the endosomal sorting complex protein Vps32, which is essential for both the pH response and the virulence of

*C. albicans* (Cornet et al. 2005). Similarly, expression of ferric reductase genes occurs downstream of Rim101 activation in *C. albicans* (Baek et al. 2008). This connects the pH response to known virulence factors and is probably one reason why PacC/Rim101 mutants show decreased virulence. Mucosal invasion by *C. albicans* requires degradation of epithelial cell junctions by the protease Sap5p, which is upregulated downstream of Rim101. Expression of Sap5p in a Rim101 mutant strain restored the ability of *C. albicans* to invade an epithelial barrier in an *in vitro* model (Villar et al. 2007). Changes in cell wall composition also occur downstream of Rim101 activation in *C. albicans*, with over-expression of several cell wall-modulating proteins partially restoring virulence to a Rim101 mutant strain (Nobile et al. 2008). These results indicate the importance of pH sensing in fungal adaptation to mammalian hosts and highlight components of the pH signaling cascade as potential drug targets.

On the other hand, calcineurin, Crz1, and Crz2 are required for the growth of *C. albicans* at acidic pH. In fact, Crz1 and Crz2 act together to enhance the growth at acidic pH (Davis 2009).

## *6.3 Gas Tension*

### 6.3.1 Carbon Dioxide

During human infection, fungi are exposed to carbon dioxide ($CO_2$) concentrations from low atmospheric $CO_2$ on epithelial surfaces to higher physiological $CO_2$ within host tissues. Work in *C. albicans* identified both carbonic anhydrase (CA) and adenylyl cyclase (AC) as $CO_2$ sensors. Conversion of atmospheric $CO_2$ to bicarbonate by CA is crucial for fatty acid biosynthesis and growth. Physiological $CO_2$ levels spontaneously generate enough bicarbonate for both growth and stimulation of AC. This activates the cAMP pathway and begins filamentation and expression of virulence traits (Bahn and Muhlschlegel 2006). Simultaneously, CA is required for virulence in models with ambient $CO_2$ levels, such as *C. albicans* epithelial invasion (Klengel et al. 2005). In contrast, CA is dispensible and AC is important in models with increased $CO_2$, like systemic infections by *C. albicans* (Bahn et al. 2005; Klengel et al. 2005; Mogensen et al. 2006).

### 6.3.2 Oxygen

In order to maintain metabolic and biosynthetic functions in the host, fungal pathogens must also be able to adapt to hypoxia within host tissues. Oxygen levels in mammalian tissues are below atmospheric levels. Furthermore, inflammation, thrombosis, and necrosis accompanied with infection are thought to rise degrees of hypoxia. In *C. albicans*, the response to hypoxia depends on the coordination of specific transcriptional regulators. In hypoxic conditions, the transcription factor Ace2 represses oxidative metabolic processes and promotes filamentation (Mulhern

et al. 2006). The transcriptional regulator Egf1p, however, antagonizes Ace2 by repressing filamentation during hypoxia (Setiadi et al. 2006). The hypoxic environment of the vaginal mucosa has been shown to induce iron uptake protein expression, probably linking the hypoxic response to both iron acquisition and virulence in *C. albicans* (Sosinska et al. 2008).

## *6.4 Nutrients*

### 6.4.1 Carbon Metabolism

Like most fungi, *C. albicans* uses sugars, especially glucose, as the preferred carbon source. While, a wide variety of nonfermentable carbon sources may also satisfy cellular requirements, including but not restricted to ethanol, acetate, glycerol, amino acids, and fatty acids. Collectively, these compounds are sometimes known as nonpreferred or alternative carbon sources since fungi only use them in the absence of sugars. These alternative sources are metabolized by three main pathways: β-oxidation of fatty acids, the glyoxylate cycle, and gluconeogenesis (Ramirez and Lorenz 2007). The main goals of these three interconnected pathways are to provide energy, replenish tricarboxylic acid (TCA) cycle intermediates and acetyl-coenzyme A (CoA), and ultimately convert lipids to acetate to glucose (Lorenz and Fink 2001; Lorenz et al. 2004).

Due to the fact that alternative carbon metabolism in *C. albicans* are important during systemic infections, deletions of genes encoding key enzymes in each pathway, the -oxidation multifunctional protein (FOX2), isocitrate lyase (ICL1), and fructose-1, 6-bisphosphatase (FBP1) in the pathways of β-oxidation of fatty acids (FOX2), the glyoxylate cycle (ICL1), and gluconeogenesis (FBP1) allow virulence defects from moderate to severe (Ramirez and Lorenz 2007). Therefore, alternative carbon metabolism in *C. albicans* plays an important role in survival within the host. On the other hand, some aspects of alternative carbon metabolism are unique to microorganisms, the identification of relevant carbon sources *in vivo* may highlight enzymes or pathways as attractive candidates for antifungal drug discovery.

### 6.4.2 Iron Acquisition

Generally, Iron is required for the survival of most organisms, primarily due to its role as a cofactor in essential metabolic functions (Lan et al. 2004). However, within the mammalian host environment, iron is sequestered away from microbes by iron carrier proteins, being stored in intracellular ferritin complexes; the trace amounts of extracellular iron bound by transferrin in the tissues and lactoferrin on mucosal surfaces and body secretions (Davis 2009), creating an iron-limited environment in which fungal pathogens must encode mechanisms for iron acquisition in order to survive (Haas et al. 2008).

Many fungi possess high affinity iron chelators, called siderophores, which efficiently bind host iron in the extracellular space and store it within the fungal cytoplasm. Fungal pathogens must also possess mechanisms for controlling and coordinating the utilization of acquired iron. For instance, *C. albicans* has multiple mechanisms for utilizing iron sources from the environment, including a reductive pathway and transport of heterologous siderophores. Moreover, Als3, an adhesin, binds to ferritin, enabling its use as a source of iron (Ding et al. 2011). The recent identification of the transcriptional regulator Hap43 in *C. albicans* has provided view for a mechanism by which *C. albicans* can adapt to iron limitation by reducing iron utilization. Hap43 was found to act as a transcriptional activator for the ferric reductases, which are crucial for the removal and utilization of iron from chelators including both siderophores and host carrier proteins (Baek et al. 2008). A novel mechanism by which *C. albicans* scavenges iron from host hemoglobin was also recently described. Receptor mediated endocytosis of hemoglobin facilitates extraction of iron, probably by a heme oxygenase in the vacuole (Weissman et al. 2008). Some Bcr1 targets in *C. albicans* play a role in acquiring iron from host proteins. These include two CFEM proteins, Rbt5 and Pga10, which act as receptors for hemoglobin, allowing endocytosis of the host iron complex (Ding et al. 2011). This hemoglobin utilization system considered an additional iron acquisition system that will probably be linked to survival of *C. albicans* within the host.

In addition to the specific sensory and regulatory adaptation mechanisms briefed above, *C. albicans* pathogens must also adapt to changes in nitrogen, calcium, magnesium, and copper sources, pressure, and fluid flow rates.

## 7 Prevention of Candidiasis

In general, like other fungal infections, most *Candida* infections can be prevented by keeping the skin clean, dry, and free from abrasions or cuts. Moreover, by using antibiotics according to doctor's directions since our bodies contain Acidophilus bacteria as a normal flora in the gut and this friendly bacteria helps keep our body in balance and able to fight pathogenic bacteria and fungus, like *Candida*. Uncontrolled intake of antibiotics may kill *Acidophilus* bacteria and enhance *Candida* growth. On the other hand, resistance of *Candida* to the used antifungal drugs can be decreased by following the doctor's directions and taking the described antibiotic completely. Furthermore, following a healthy lifestyle, including proper nutrition ensures good immunity. People with diabetes should try to keep their blood sugar under tight control since sugars are food for *Candida* and promote its growth.

## 8 Treatment of Candidiasis

Now a day, several antifungal agents are available, these include: Polyene derivatives such as Amphotericin B, Lipid based amphotericin, Nystatin, Azoles, and Griseofulvin. Amphotericin B is a polyene antimycotic, has been the drug of choice for most systemic

fungal infections. It has a greater affinity for ergosterol in the cell membranes of fungi than for the cholesterol in the host's cells; once bound to ergosterol it causes disruption of the cell membrane and death of the fungal cell. Amphotericin B is usually administered intravenously, often for 2–3 months. The drug has side effects of being toxic; thrombo-phlebitis, nephrotoxicity, fever, chills and anemia frequently occur during administration. Although newer drugs have been shown to be as efficacious and less toxic, amphotericin B is still the gold standard for comparison as well as the therapy of last resort for severe infections. However, Lipid based amphotericin is effective, less toxic, and more expensive (Khan and Jain 2000; Di salvo 2007). Next, nystatin is considered the drug of choice for vaginitis and cutaneous infections (Hector 1993). On the other hand, the azoles (imidazoles and triazoles), including ketoconazole, fluconazole, itraconozole, voriconazole and posaconazole are being used for muco-cutaneous candidiasis, dermatophytosis, and for some systemic fungal infections. The general mechanism of action of the azoles is the inhibition of ergosterol synthesis which affects cell wall synthesis. Oral administration and reduced toxicity are distinct advantages. Griseofulvin is a very slow-acting drug which is used for severe skin and nail infections. Its effect depends on its accumulation in the *stratum corneum* where it is incorporated into the tissue and forms a barrier, which stops further fungal penetration and growth. It is administered orally (Khan and Jain 2000; Di salvo 2007). New agents with different mechanisms of action are under development (Hector 1993). Echinocandins (caspofungin), a new antifungal agent recently approved by the FDA (Di salvo 2007). Importantly, it is active against *Candida* isolates that are refractory to azole treatment. It kills fungi by inhibiting the synthesis of ß-1, 3-glucan, a major component of the fungal cell wall. Thus, it has potent *in vitro* activity against *C. albicans* biofilms (Bachmann 2002).

Recently, thousands of products have been screened *in vitro* for antimicrobial activity and promising molecules have been evaluated in various animal models for new drug development. Much research focuses on plant sources.

## 9 Conclusions and Future Recommendations

During growth within the intestinal tract, *C. albicans* senses pH, oxygen, carbon sources, and the presence of surfaces allowing it to optimize gene expression for a particular environment. With these mechanisms for sensing, *C. albicans* is able to efficiently survive in humans starting from infancy, establishing itself in its most important natural niche.

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