Minireview Article

NEWLY EMERGING *CANDIDA* SPECIE: SHOULD CLINICIANS AND MYCOLOGIST BE CONCERNED?

ABSTRACT

C. auris recently emerged as a global nosocomial pathogen associated with multidrug resistance and high mortality rates. Although animal studies indicate that *C. auris* has reduced pathogenicity and virulence compared to *C. albicans*, this emerging pathogen appears to be far more able to induce systemic infection and mortality than other potential multi drug resistance (MDR) yeast pathogens. Issues with regard to the identification of *C. auris* using both phenotypic and molecular techniques have raised concerns about detecting the true scale of the problem. This mini- review considers the literature available on *C. auris* and highlights the mechanism of pathogenesis and antifungal resistance, which will provide direction for further work in this field.

KEYWORDS: *Candida auris*, emerging infection, nosocomial pathogens, antifungal susceptibility, pathogenesis

Annually, an estimated 1.5 million people die from invasive fungal infections (Brown *et al*., 2012). The advance of life expectancy, the rise of immunosuppressive treatments, higher survival of patients living with cancer or chronic disease and the use of catheters are all factors that attributed to the emergence of opportunistic fungal pathogens over the last decades (Pfaller, 2000; Pappas, 2018). Candida albicans is recognized as the main causative pathogen of candidiasis (Brown *et al.*, 2012). However, new species are on the rise, with the globally emerging multidrug-resistant *Candida auris* as one of the most concerning examples.

Candida auris is a recently identified multi-drug resistant *Candida* species, first reported in 2009 from the ear canal of a 70 year old female Japanese patient in Tokyo (Satoh *et al., 2009*). Treatment options of *C. auris* are limited due to antifungal resistance, misidentification and its ability to persistently colonize hospital environments. It has been associated with infections and outbreaks in healthcare settings in Europe, Asia, North America, South America, and Africa (Lockhart *et al*., 2017, Clancy and Nguyen, 2017). Recent reports have demonstrated that *C. auris* usually expresses fewer virulence factors than does *Candida albicans*. However, the tendency of *C. auris* transmission within and between healthcare facilities is unique among *Candida* spp. and is possibly promoted by virulence and pathogenicity factors that facilitate skin colonization and environmental persistence (Luana and Arnaldo, 2018).

The complete genome of *C. auris* was only recently investigated (Chatterjee et al., 2015; Sharma et al., 2015), and we are far from fully understanding the role of different genes in the pathogenicity and virulence of this emerging pathogen. The main problem is that the *C. auris* genome sequence contains many uncharacterized and hypothetical proteins, and it is unclear whether these proteins are involved in species-specific characteristics that promote its aggressiveness as a pathogen (Chatterjee et al., 2015). This mini-review will attempt to provide information regarding the pathogenesis and mechanism of antifungal resistance in *C. auris.*

PHENOTYPIC TRAITS AND IMPLICATIONS FOR PATHOGENICITY

Phenotypic switching and morphogenesis are well-known virulence attributes of *C. albicans* (Polke et al., 2015). *C. albicans* deploys two typical switching systems, namely the morphological yeast filament transition and phenotypic white-opaque switching. Recently, Bentz and co-workers (Bentz *et al*., 2018) reported phenotypic switching in *C. auris* when cultured onto CHROMagar Candida, on which C. albicans and C. tropicalis can be relatively reliably identified via a colony color change (C. albicans—green, C. tropicalis—navy blue). Other clinically relevant Candida species, including *C. auris*, will have a pale appearance. Further culturing of *C. auris* on CHROMagar Candida led to the description of three predominant colony types: white, pale and sectored (dark purple). No texture changes were observed, as all colonies displayed a smooth and glossy phenotype (Bentz *et al*., 2018).

The ability to produce hyphae is thought to promote virulence by giving the fungus the ability to invade epithelial cell layers by exerting mechanical force, breaching and damaging endothelial cells, and causing lysis of macrophages and neutrophils following phagocytoses (Thompson *et al.,* 2011).

Although micromorphological studies of *C. auris* colonies suggest that this pathogen does not produce germ tubes, pseudohyphae or chlamydospores (Lee et al., 2011; Chowdhary et al., 2014; Borman et al., 2016; Wang et al., 2018), this yeast may present pseudohyphae-like forms under high-salt stress (Wang et al., 2018) and, occasionally, in the biofilm community (Sherry et al., 2017). Pseudohyphae-like forms are characterized by rudimentary growth, with an elongated shape and incomplete cell division (Sherry et al., 2017; Wang et al., 2018). Indeed, comparative genome analyses have confirmed that *C. auris* and closely related species do not have two genes, candidalysin (*ECE1*) and hyphal cell wall protein (*HWP1*), both of which are highly expressed in *C. albicans* and the transcription of both is strongly associated with hyphal formation (Munoz et al., 2018).

C. auris fails to form chlamydospores after growth on cornmeal agar when incubated for 3 days at 30°C and does not germinate when incubated with fetal bovine serum (FBS). This fact was confirmed in the *Galleria mellonella* model of infection of *C. auris*, during which the isolates did not undergo significant filamentation at 18 h or at any time post infection (Borman et al., 2016).

An interesting observation regarding the growth of *C. auris* is that certain isolates grow in clumps (i.e., budding occurs, but daughter cells are not released), which results in large aggregates of organisms that cannot be easily disrupted *in vitro* (Borman et al., 2016). These isolates are called "aggregate" strains, and certain aggregate strains are too large for *G. mellonella* larval inoculation, hindering accurate yeast cell counting.

Yeast cell aggregates were also observed in the kidneys of mice infected with *C. auris*, suggesting that aggregation might be a mode of immune evasion and persistence in tissues, which warrants further investigation (Ben-Ami et al., 2017). Taken together, phenotypic switching in *C. auris* could have important implications for its pathogenicity, virulence, sexual reproduction and ability to colonize distinct host niches, which warrants further investigation.

TOLERANCE TO THERMIC AND OSMOTIC STRESSES

Survival and growth at physiologic temperature are prerequisites for microbial invasion and pathogenicity. *C. auris* exhibits thermotolerance, growing optimally at 37°C and maintaining viability up to 42°C. In addition, this pathogen is salt tolerant, and cells aggregate into large, difficult-to-disperse clusters, which may promote persistence in the hospital environment (Satoh et al., 2009; Borman et al., 2016). The ability of *C. auris* isolates to grow at 37°C and 40°C appears to be similar to that of *C. albicans*, and certain isolates also grow at 42°C (Ben-Ami et al., 2017). *C. auris* can also grows at high temperature (40°C) and salinity (10% wt/vol) when cultured in Sabouraud (SAB) or yeast nitrogen base (YNB) broth with dulcitol or mannitol as the carbon source (Welsh et al., 2017).

IMPORTANCE OF LYTIC ENZYMES FOR FUNGAL INVASIVENESS

The production of extracellular hydrolytic enzymes has been recognized as an important virulence trait contributing to the pathogenicity of Candida species. Proteinases are by far the most commonly virulence associated enzymes. In addition, also hemolysins, lipases and phospholipases seem to play a crucial role. Secreted aspartyl proteinases (SAPs) are one of the most significant extracellular enzymes produced in C. albicans. Classically, these enzymes were considered to play a role in the degradation of host tissue to provide nutrients for pathogen propagation. However, in recent decades, proteinases have also been associated with cell wall maintenance, the formation of polymicrobial biofilms, adhesin to external protective barriers of the host, deregulation of the complement system, inactivation of host antimicrobial peptides, evasion of the immune responses and the induction of inflammatory mediator release from host cells (Rapala-Kozik *et al.,2018;* Naglik *et al.*, 2003). In fact, a recent study conducted by Wang et al. (2018) demonstrated that the level of aspartyl proteinase (Saps) secreted by *C. auris* isolate at 42°C was higher than that exhibited by *C. albicans* at the same temperature (Wang et al., 2018). These findings suggest that *C. auris* isolates are not only well adapted to temperature stress but also maintain their pathogenicity at higher temperatures.

Hydrolases are the largest group of enzymes (42%) found in the *C. auris* (strain 6684) genome, followed by transferases (25%) and oxidoreductases (19%) (Chatterjee et al., 2015). Furthermore, comparative genome analyses have revealed similar numbers of lipases in the *C. auris* relative to those of C. *albicans* and *C. dubliniensis* (Munoz et al., 2018). The ability to produce lytic enzymes has been demonstrated in *C. auris* isolates, and the production of these enzymes is strain dependent (Kumar et al., 2015; Larkin et al., 2017).

Similarly, most strains displayed hemolysin activity, conferring a high capacity for iron acquisition, growth, and invasiveness leading to widespread infection (Tsang et al., 2007; Kumar et al., 2015). Secretion of hemolysins is considered to promote survival within the mammalian host by allowing assimilating iron from the hemoglobin-heme group (Furlaneto *et al*., 2018). Many common pathogenic Candida species display hemolysin activity, including C. albicans, C. dubliniensis, C. glabrata and C. tropicalis (Furlaneto *et al*., 2018; Rossoni *et al*., 2003; Luo *et al*., 2001; Seneviratne *et al*., 2011). Hemolysin production seems to be higher in strains isolated from hospital infections compared to those from environmental sources, indicating this trait to be an important virulence factor (Brown *et al*., 2012). In *C. auris*, hemolysin production was also observed (Kumar *et al*., 2015). Nonetheless, this was a single isolate only and variation in hemolysin activity between the different *C. auris* clades still needs to be evaluated.

Production and secretion of a wide variety of enzymes is likely to contribute to rapid spread of *C. auris*. However, further investigation is warranted to reveal to which extend these enzymes are involved in *C. auris* virulence and pathogenicity.

CANDIDA AURIS AND ITS ALARMING ABILITY TO PERSISTENTLY COLONIZE HUMAN HOST AND THE ENVIRONMENT

Studies have demonstrated the ability of *C. auris* to colonize and spread throughout hospital environments. One of the most alarming characteristics of *C. auris* is the ability of this yeast to adhere to and persist on abiotic surfaces, including dry and moist surfaces, bedding material, floors, sinks and beds, as well as human skin, ears, and nasal cavities (Schelenz et al., 2016; Piedrahita et al., 2017; Vallabhaneni et al., 2017; Welsh et al., 2017).

Nosocomial *C. auris* outbreaks have been reported in hospitals all around the world, some of them persisting up to 16 months (Vallabhaneni *et al*., 2017). Moreover, *C. auris* supposedly has the ability to cause low-grade disease years after colonization. Heath et al. (2019) described a case of *C. auris* sternal osteomyelitis in a patient who was colonized by *C. auris* 3 years prior clinical disease manifestation.

Although the ecological niches of *C. auris* remain unidentified, environmental sampling within the hospital environment has demonstrated *C. auris* to colonize and persist on abiotic surfaces such as bedding material, floors, sinks, as well as human skin, ears and nasal cavities (Vallabhaneni *et al*., 2017, Piedrahita *et al*., 2017). After a period of 7 days, *C. auris* recovery from dry or moist surfaces was shown to be similar to that of other clinically relevant Candida

species, including C. albicans, C. glabrata and C. parapsilosis (Piedrahita *et al*., 2017). Additionally, it was shown that *C. auris* is able to remain viable for at least 14 days on a plastic health care surface, as measured by colony forming units (CFU) (Welsh et al., 2017).

Even though *C. auris* seems to be able to colonize plastic health care surfaces, this fungus shows a weak adherence ability to catheter surfaces made of silicone elastomer, compared to C. albicans (Larkin *et al*., 2017). Implying a reduced number of catheter-associated candidiasis caused by *C. auris* relative to C. albicans. Several (review) articles report suboptimal efficacy of commonly used hospital environment disinfectants against *C. auris* as one of the factors contributing to its persistence within the hospital environment. However, multiple original studies show high efficacy of a plethora of commercially available disinfectants against *C. auris* compared to C. albicans (Rutala *et al*., 2019, Abdolrasouli *et al*., 2017, Cadnum *et al*., 2017). Only quaternary ammonium-based disinfectants seem to be significantly less effective against *C. auris*, but also against C. albicans and C. glabrata (Cadnum *et al*., 2017). However, most studies did not assess the efficacy of disinfectants on hospital surfaces and other materials commonly found in hospital settings, such as fabrics and polymer. To establish effective infection prevention protocols preventing the transmission of *C. auris* via contaminated surfaces, examination of *C. auris* disinfection on this kind of surfaces is needed.

BIOFILM PRODUCTION LEADING TO ANTIFUNGAL RESISTANCE

Many microbes are found in biofilm ecosystems. The biofilm forms a structured microbial community encased in a matrix of exopolymeric material. Biofilms are a common form of microbial growth that is crucial for the development of a broad spectrum of infections in the human host and also for defending pathogens from phagocytes and antimicrobial drugs (Fanning and Mitchell, 2012). Seven highly conserved genes (*PLB3*, *IFF4*, *PGA52*, *PGA26*, *CSA1*, *HYR3*, and *PGA7*) are upregulated during biofilm production across isolates representative of *C. auris*, *C. haemulonii*, *C. duobushaemulonii*, and *C. pseudohaemulonii*. The same proteins are associated with biofilm production and mechanisms of antifungal resistance in *C. albicans* strains (Kean et al., 2018). The *C. auris* biofilms mostly consists of budding yeasts and occasionally pseudohyphae embedded in a limited amount of extracellular matrix. C. albicans biofilms are formed by densely packed hyphae and yeast cells embedded in extracellular matrix, whereas C. glabrata forms a thin biofilm with yeast cells only, lacking extracellular matrix (Sherry *et al*., 2017).

Candida biofilms show intrinsic resistance against antifungals. Several mechanisms were proposed to contribute to this resistance: (1) the high cell density within the biofilm; (2) decreased growth rate and nutrient limitation; (3) sequestration of drugs by the extracellular matrix (ECM); (4) the high expression of resistance genes, especially those encoding efflux pumps; and (5) the presence of ‘persister’ cells (Ramage*et al*., 2005). Also *C. auris* biofilms

display lower susceptibility against antifungals, including caspofungin, micafungin and amphotericin B (Sherry *et al*., 2017).

CONCLUSION

C. auris recently emerged as a global nosocomial pathogen associated with multidrug resistance and high mortality rates. Although animal studies indicate that *C. auris* has reduced pathogenicity and virulence compared to *C. albicans*, this emerging pathogen appears to be far more able to induce systemic infection and mortality than other potential MDR yeast pathogens, such as *C. glabrata* and *C. haemulonii* (Fakhim et al., 2018). This finding is likely to be related to the tolerance of *C. auris* strains to osmotic and high-temperature stress as well as to its ability to produce several lytic enzymes and biofilm (Ben-Ami et al., 2017; Welsh et al., 2017).

However, the origin of this unprecedented emergence remains unclear. Genomic analyses revealed *C. auris* possesses many genes associated with virulence and reduced antifungal susceptibility, including genes encoding secreted aspartyl proteases, lipases, phospholipases, hemolysins and drugs efflux pumps (Chatterjee *et al*., 2015, Munoz *et al*., 2018, . Pappas *et al*., 2018). Nonetheless, many genes are still uncharacterized and further investigation is required to understand the molecular mechanism responsible for the high pathogenicity and antifungal resistance of this pathogen.

An important limitation of virulence analyses based on clonal strains cultured from patients during outbreaks is that it remains unclear whether such findings may be safely extrapolated to all isolates of the species or whether they are only representative of biological properties exhibited by a few clonal strains.

An additional point that deserves more attention is the characterization of adhesins and other molecules responsible for the capability of *C. auris* to persistently colonize abiotic and biotic surfaces. Indeed, this pathogen is able to survive and persist under different environmental conditions, including on dry materials, bedding material, floors, sinks and beds, and it exhibits tolerance to temperature and osmotic stresses (Ben-Ami et al., 2017; Welsh et al., 2017).

In conclusion, *C. auris* expresses many important virulence traits, including traits that are well characterized in other Candida species, and seemingly unique traits, such as the ability to evade the innate immune system and persistently colonize the skin of human host. This together with the high propensity to develop resistance to multiple antifungals likely contributed to its emergence as a nosocomial pathogen.

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