International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Review Article

Biofilm Formation in *Candida* Infections - A Review

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ABSTRACT

Biofilms are the most common mode of microbial growth in nature and are important in clinical infections, especially due to the high antibiotic resistance associated with them. Fungi most commonly associated with such disease are in the genus *Candida*, most notably *Candida albicans*. Non albicans *Candida* species also are attracting considerable interest because they are known to be important agents of hospital acquired infections. Studies on Biofilms consider them as structures composed of a community of microorganisms belonging to the same or different species. The community formed by the fungus *C. albicans* is composed of three morphological types, yeasts, pseudohyphae, and hyphae. The advantages of biofilm formation include protection in the environment, resistance to chemical and physical removal, and ability of colonizing and causing infection due to drug resistance and evasion to host immunity. As medical device-associated *Candida* infections are highly drug resistant and may lead to serious complications, there is a need for continuous surveillance of these infections to initiate preventive and therapeutic measures. Photodynamic antimicrobial chemotherapy is a new development that has been successfully used against *C. albicans* biofilms. It remains to be seen whether resistance would become a major issue if photodynamic therapy becomes widely adopted. Other promising alternative therapies with different mechanisms of action include phyto therapy, disruptors of extracellular matrix by enzymes, signaling molecules, antimicrobials, combined therapies, and so on. The results from these trials will hopefully be positive and offer new ways to minimize the burden of biofilm infection.

Key words: Biofilm, *Candida* sp., drug resistance, Photodynamic antimicrobial chemotherapy.

INTRODUCTION

Biofilms are the most common mode of microbial growth in nature and are important in clinical infections, especially due to the high antibiotic resistance associated with them. [1] The clinical trials indicate the importance of the biofilm [2] because they are common on implanted medical devices, and it contributes to most of the nosocomial infections. [3]

Transplantation procedures, immune suppression, the use of chronic indwelling devices, and prolonged intensive care unit stays are recognized to have increased the prevalence of fungal disease. It is well known that the fungi most commonly associated with such disease are in the genus *Candida*, most notably *Candida albicans*, which causes both superficial and systemic disease. Even with current antifungal therapy, mortality of patients with invasive candidiasis is increasing. Candidiasis is generating considerable interest because it is usually associated with indwelling medical devices (e.g., dental implants, catheters, heart valves, vascular bypass grafts, ocular lenses, artificial joints, and central nervous system shunts), which can act as substrates for biofilm growth. [1, 4]

Non albicans *Candida* species also are attracting considerable interest because they are known to be important agents of

hospital acquired infections. Many of these are implant-associated infections in which the micro-organisms form biofilms on the surfaces of catheters, joint replacements, prosthetic heart valves and other medical devices. [5]

A striking feature is that when fungi exist as a biofilm, they are less susceptible to antibiotics. The main problem of Biofilms is in the contamination of medical devices and in the infection of wounds. [6] This article reviews the current literature in terms of existing strategies for treating biofilm infections, which are developed to prevent and treat biofilm infection of medical devices and wounds.

Biofilm Formation

Studies on Biofilms consider them as structures composed of a community of microorganisms belonging to the same or different species. Bacteria, yeasts and filamentous fungi are able to form communities on both biotic and abiotic surfaces. *C. albicans* forms a heterogeneous biofilm structured in an extracellular matrix containing yeasts, pseudohyphae and hyphae on mucosal surfaces and medical devices that cause diseases and dissemination of infection. [7]

***Candida albicans* biofilm structure**

The community formed by the fungus *C. albicans* is composed of three morphological types, yeasts, pseudohyphae, and hyphae. The polymeric substances are constituted by polysaccharide, proteins, hexosamines, uronic acid, and DNA, and they are required to promote adherence and biofilm formation, protect the fungal cells against phagocytosis, maintain biofilm integrity and limit substances diffusion.

The biofilm growth condition is coordinated by events divided into four stages: early stage, the yeasts adhere to the substrate forming the biofilm scaffold, following by cell coaggregation and colonization. Then, at intermediate stage, the cells grow and proliferate forming the basal layer anchoring the cells. Next, the adherence to the surface stimulates the transition from yeast to hyphae and production of pseudohyphae and, finally, at the mature stage the tridimensional structure enlarges and yeasts cells on the top of biofilm disseminate to distant sites to initiate the cycle. [7] The biofilm can expand and mature. Once nutrients are diminished and waste products have accumulated, cells begin to be released as biofilms disperse. [6] Dispersion of yeast cells from the mature biofilm directly contribute to virulence. [8]

The advantages of biofilm formation

The advantages of biofilm formation include protection in the environment, resistance to chemical and physical removal, and ability of colonizing and causing infection due to drug resistance and evasion to host immunity.

As a community of microorganisms, the fungal cells are able to communicate and coordinate the activities of the biofilm by secretion of signaling molecules in a process named quorum sensing. Quorum sensing contributes to control the competition for nutrients, to protect the population and has important clinical implication for dissemination of infection on distant sites.

Farnesol and tyrosol are the two most studied signaling molecules. They have contrary functions, for example, when farnesol accumulates beyond the level, it inhibits the yeast-to-hyphae conversion, but it is unable to block hyphae extension or reverse germ tube formation. Farnesol is secreted at later stages of biofilm formation and stimulate dispersion of cell.

On the other hand, tyrosol acts at the first stage of biofilm formation stimulating filamentation and biofilm formation. The transition from yeast to hypha form is crucial for biofilm formation and pathogenicity, but the reverse process allows the colonization of distal sites by dispersion of yeast cells in case of nutrient starvation and presence of toxic products. [7] The dispersion of cells initiates around 3 hours after incubation and reaches the maximum at 24 h of growth. [9]

Candida biofilm resistance is a multifactorial phenomenon, with various mechanisms acting together during the

different stages of biofilm growth. *Candida albicans* produces and releases more quorum-sensing molecules (QSMs) in formed biofilms. A mature C. albicans biofilm displays more antifungal resistance than an early biofilm. Production of an extracellular matrix (ECM) is also one of the key resistance mechanisms for *Candida* biofilms. The ECM of *Candida* biofilms consists of extracellular polymeric substances, including carbohydrate and extracellular DNA (eDNA), and these components have been linked to multidrug resistance. [9]

The clinical challenge by biofilms

Biofilms formed by *C. albicans* are resistant to fluconazole and sensitive to high concentrations of amphotericin B. It has also been demonstrated resistance to the antifungals voriconazole, nystatin, terbinafine and ravuconazole. [7] As a result, implant infections are difficult to treat and usually the implant have to be removed. [5, 10]

As medical device-associated *Candida* infections are highly drug resistant and may lead to serious complications, there is a need for continuous surveillance of these infections to initiate preventive and therapeutic measures. [9]

Strategies for treating biofilm infections

Photodynamic antimicrobial chemotherapy (PACT) is a new development that has been successfully used against *C. albicans* biofilms. This therapy is mediated by a dye called photo sensitizer that is excited by a light source, e.g. laser, light emitting- diode (LED), and white light, producing reactive oxygen species (ROS) and free radicals. The clinical uses of blue light are still being developed, but effective action against biofilms and low toxicity suggest that this may be a useful therapy to treat infected wounds or other sites, which can be irradiated. Clinical evidence has not identified any side effects from application of blue light to humans. This approach is a relatively cheap and non-toxic method. One advantage of the use of PACT is equivalent activity against both drug resistant and sensitive pathogens, as the mechanisms of antibiotic resistance do not affect the efficacy of photo inactivation. The great advantage of this therapy is that the microbial cells have no resistance mechanisms against the PACT- produced products. Ultraviolet light is not suitable for application to humans due to mutagenic properties. Moreover, there are other promising alternative therapies with different mechanisms of action that include phytotherapy, disruptors of extracellular matrix by enzymes, signaling molecules, antimicrobials, combined therapies, and so on. [7] It remains to be seen whether resistance would become a major issue if photodynamic therapy becomes widely adopted. [6]

CONCLUSION

As numbers of devices and wound infections increase in population, the need for new developments to reduce the impact of biofilm infections becomes more urgent. Promising approaches to address this need are being developed and clinical trials are running. The results from these trials will hopefully be positive and offer new ways to minimize the burden of biofilm infection.

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How to cite this article: Kavitha MK. Biofilm formation in *candida* infections - a review. Int J Health Sci Res. 2019; 9(1):236-239.

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