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The Role of ALS3 Gene in C. albicans Biofilm and Its Management Strategies: A Literature Review

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ABSTRACT

Candida albicans is an opportunistic fungus that can cause infections in humans, ranging from mild mucosal infections to life-threatening systemic infections. One of the key factors in the pathogenesis of C. albicans is its ability to form biofilms, a structure that provides protection against the immune system and antifungal treatments. Biofilm formation involves the interaction between fungal cells and a complex extracellular matrix, as well as adhesion genes such as ALS3. The ALS3 gene encodes the Als3 protein, which plays a role in the adhesion of C. albicans cells to surfaces and the morphological transition from yeast to filamentous form, both of which are crucial for biofilm stability. Anti-biofilm therapies targeting the ALS3 gene or the extracellular matrix have the potential to enhance the effectiveness of C. albicans treatment and reduce resistance to antifungal therapies. A deeper understanding of biofilm formation mechanisms in C. albicans will open up opportunities for the development of more effective therapies to address this fungal infection, particularly in patients with compromised immune systems.

Keywords: C.albiacans; biofilm; Als3

INTRODUCTION

Fungal infections caused by Candida species have become a significant health problem worldwide. One of the most commonly associated species with infections in humans is Candida albicans. Naturally, C. albicans colonizes various parts of the human body, such as the oral cavity, gastrointestinal mucosa, and genital mucosa, without causing disease symptoms (Vila et al., 2020). Under normal conditions, C. albicans exists as a commensal organism in the body but can transform into a pathogen when there is disruption in the host immune system, changes in body microbiota, or other environmental factors. These changes can trigger C. albicans to develop into a pathogen that causes a range of infections, from mild mucosal and skin infections to life-threatening systemic infections (Denning & Bromley, 2015; Perfect, 2017).

One crucial aspect of C. albicans pathogenesis is its ability to form biofilms, a structure that enables microorganisms to survive in unfavorable environments, including the presence of the immune system and antifungal treatment. Biofilms consist of microbial cell communities that adhere to surfaces or substrates and are surrounded by a complex extracellular matrix (Kioshima et al., 2019). The biofilm formation process in C. albicans involves interactions between fungal cells, the extracellular matrix, and components of the host body, creating a three-dimensional structure that provides protection from external factors (Brown et al., 2012). This biofilm also enhances C. albicans virulence, as cells within the biofilm exhibit different properties compared to C. albicans cells in their planktonic state, including increased resistance to antifungal therapies and immune system effects (Wong et al., 2014).

Biofilm formation in C. albicans is influenced by various genetic factors, one of which is the expression of the ALS3 gene (Agglutinin-Like Sequence). The ALS3 gene encodes a protein involved in the adhesion of C. albicans cells to host surfaces and in the morphological transition from the yeast form to a more invasive filamentous form. This morphological change is crucial for the formation of a more stable biofilm structure and for increasing the pathogenicity of C. albicans (Sadowska et al., 2016). Additionally, other proteins in the ALS family, such as Als3, play a role in the initial adhesion process and biofilm stability, enabling the fungus to persist on host surfaces or tissues for extended periods (Liu et al., 2021).

Recent studies have further revealed that biofilms not only enhance C. albicans resistance to treatment

but also facilitate chronic infections. Biofilm formation can occur in various clinical conditions, such as oral mucosal infections in denture users, urinary tract infections, and systemic infections in immunocompromised patients (Nazzaro et al., 2017). By understanding the mechanisms of biofilm formation in C. albicans and the genes involved, such as ALS3, we can develop more effective treatment strategies to combat this fungal infection, either by inhibiting biofilm formation itself or by improving the host's immune response to the fungus (Fazly et al., 2013).

This literature review aims to discuss the role of adhesion genes, particularly ALS3, in biofilm formation in C. albicans, as well as the mechanisms of biofilm formation and the potential anti-biofilm therapies that may help address C. albicans infections associated with biofilms.

DISCUSSION

Biofilm Formation in Candida albicans

Biofilms in Candida albicans are highly complex structures that can form on various biotic and abiotic surfaces, including human tissues. The formation of biofilms in C. albicans begins with the adhesion of fungal cells to a specific surface, which is influenced by various genetic and environmental factors. One of the key genes involved in this early stage is ALS3 (Agglutinin-Like Sequence), which encodes the Als3 protein. This protein acts as a bridge between C. albicans cells and the surface substrate, whether it is host cells or artificial surfaces. Als3 induces the transition from the yeast form (blastospore) to the more invasive filamentous form (hyphae), a critical element in forming a stable biofilm and facilitating long-term colonization (Sadowska et al., 2016; Sadowska et al., 2016).

The first step in biofilm formation in C. albicans involves the adhesion of C. albicans cells to one another and to biotic or abiotic surfaces. This step is crucial and pivotal for all subsequent stages of biofilm development in C. albicans (Uppuluri & Lopez Ribot, 2017). The Als3 protein is essential during this critical first phase. Als3's ability to bind to various host cell receptors allows C. albicans to easily attach to diverse surfaces (Liu et al., 2021). After adhesion, the fungus then changes its morphology into the hyphal form, which is vital for invasion and for creating a more stable three-dimensional structure. This hyphal form leads to the formation of a network of interconnected filaments capable of penetrating host tissues. The biofilm structure, consisting of yeast, hyphal, and filamentous forms, allows C. albicans to adapt in harsh environments that are difficult for the host immune system to reach (Marc et al., 2018).

The biofilm formation process in C. albicans is heavily influenced by environmental factors such as temperature, pH, and nutrient concentrations in the surrounding environment. For example, elevated temperatures and changes in glucose concentration can enhance biofilm formation, while unfavorable environmental conditions can inhibit its development (Brown et al., 2012). These changes in environmental factors contribute to C. albicans' ability to survive and proliferate in the human body, even under immunocompromised conditions or in the presence of antifungal drugs.

The Role of the ALS3 Gene in Biofilm Formation

One of the most important genes in biofilm formation is ALS3, which encodes the Als3 protein. This protein enables C. albicans cells to adhere to surfaces and transition into a more invasive hyphal form. Agglutinin-like sequence protein 3 (Als3), a member of the Als family, is a multifunctional adhesin that can bind to various host cell receptors. Research shows that the ALS3 gene is essential for the formation of a complete and stable biofilm structure (Kioshima et al., 2019; Liu et al., 2021). Studies have shown that deletion of the Als3 protein (als3Δ/Δ) results in the formation of biofilms with lower biomass, making the cells within the biofilm less dense and more heterogeneous. As a result, biofilms with lower cell density are more susceptible to antifungal penetration. The deletion of Als3 protein also affects the expression of other genes associated with hyphal formation and biofilm development (Liu et al., 2021). In many studies, inhibition of ALS3 expression or mutations in this gene led to a reduced ability of C. albicans to adhere to surfaces and form strong biofilms. In vivo models show that C. albicans strains unable to produce Als3 exhibit decreased invasion and virulence, which underscores the crucial role of this gene in C. albicans infection pathogenesis (Liu et al., 2021).

The reduction in ALS3 expression inhibits the morphological transition of C. albicans from the yeast form to the hyphal form, resulting in decreased biofilm formation. In various experimental models, both in vitro and in vivo, C. albicans strains lacking ALS3 function demonstrate lower adhesion levels to host surfaces and fail to form stable biofilms (Fazly et al., 2013). Therefore, ALS3 is an attractive target for research and the development of anti-biofilm therapies for C. albicans. By blocking or inhibiting the function of Als3, we can reduce its ability to form biofilms, which in turn may enhance the effectiveness of antifungal treatments.

Extracellular Matrix in Candida albicans Biofilm

The extracellular matrix in C. albicans biofilm consists of various important components, including polysaccharides such as beta-glucan, proteins, and DNA. This matrix serves as a protective layer for the cells within the biofilm against external factors, including the host immune system and antifungal therapies. One of the key components of this matrix is beta-glucan, which plays a role in enhancing the biofilm's resistance to antifungal agents. Beta-glucan also interacts with the host immune system through receptors like Dectin-1, which induces an immune response while also helping the microorganism survive in a threat-filled environment (Uppuluri & Lopez Ribot, 2017).

This extracellular matrix provides C. albicans biofilm with protection from external influences,

making it significantly more resistant to treatment than planktonic cells. This is due to the matrix's ability to limit the penetration of antifungal drugs into the biofilm, thus reducing the efficacy of the treatment. Inhibiting the production or degradation of matrix components, such as beta-glucan, can decrease the biofilm's resistance to treatment and increase its vulnerability to antifungal therapies (Wong et al., 2014; Uppuluri & Lopez Ribot, 2017). Therefore, compounds that can disrupt the extracellular matrix, such as glucanase enzymes, or those that can interfere with signaling pathways regulating biofilm formation, are critical areas in the development of anti-biofilm therapies (Nazzaro et al., 2017).

Biofilm and Resistance to Antifungal Treatment

Candida albicans biofilms are highly resistant to antifungal treatment due to the extracellular matrix that protects the biofilm cells from the effects of the drugs. Additionally, the cells within the biofilm have a different metabolic rate compared to planktonic cells, making them more resistant to drugs that target active metabolic pathways. Within the biofilm, the cells are more protected and exhibit slower responses to treatment, making it more difficult to eliminate them with antifungal therapy (Sadowska et al., 2016). The reduced metabolic activity within the biofilm also contributes to drug resistance, as most antifungal drugs work by inhibiting active metabolic pathways.

Research has also shown that C. albicans biofilms play a role in reducing the ability of antifungal drugs to penetrate and reach the cells within the biofilm. As a result, treating C. albicans infections caused by biofilms often fails, especially in patients with compromised immune systems (Sadowska et al., 2016). In this regard, effective anti-biofilm therapy will heavily depend on the development of agents that can target the extracellular matrix or specific mechanisms involved in biofilm formation and survival.

Anti-Biofilm Therapy Approaches for Candida albicans

Developing anti-biofilm therapies to address C. albicans infections that are resistant to conventional treatments is an emerging area of research. These anti-biofilm therapies involve the use of drugs or compounds that can inhibit biofilm formation or degrade the biofilm matrix, improving drug penetration into the biofilm and facilitating antifungal action against fungal cells. One promising approach is the use of small-molecule inhibitors targeting adhesion proteins like Als3. These compounds can inhibit C. albicans' ability to adhere to surfaces, which directly reduces biofilm formation (Fazly et al., 2013).

In addition, a combination approach involving both anti-biofilm therapy and antifungal treatment is becoming an attractive option. In this approach, drugs targeting biofilms work synergistically with antifungals to combat C. albicans infections. This combination can enhance drug penetration and reduce the development of resistance, ultimately improving treatment success rates (Ajdidi et al., 2019). Further research on compounds that can degrade the extracellular matrix or inhibit biofilm formation pathways could open up opportunities for more effective and efficient therapies.

Clinical Implications and the Future of Biofilm Therapy

Increased understanding of the mechanisms of biofilm formation in C. albicans offers new hope for the development of more effective therapies for fungal infections. By targeting adhesion proteins, the extracellular matrix, and signaling pathways involved in biofilm formation, we can design anti-biofilm therapies that may improve treatment success for C. albicans infections. This is especially important for immunocompromised patients or those with medical conditions that complicate treatment, such as patients with diabetes mellitus, HIV/AIDS, or those undergoing organ transplantation (Marc et al., 2018).

It is crucial to remember that the development of anti-biofilm therapies must be based on a deep understanding of C. albicans biology and the biofilms they form, as well as the environmental factors that may influence biofilm formation and resistance. In the future, it is hoped that more effective and safe anti-biofilm agents will be discovered to address the issue of antifungal treatment resistance. Approaches combining anti-biofilm therapy with immunotherapy are also an area of research that holds potential to enhance treatment effectiveness and extend the duration of fungal infection control in vulnerable patients (Wong et al., 2014).

CONCLUSION

Infections caused by Candida albicans have become one of the major health issues worldwide. The biofilm formation process by C. albicans is a key factor in the pathogenesis of this fungal infection. Biofilm formation allows C. albicans to survive in unfavorable environments, including facing the host immune system and antifungal treatments. The biofilm structure, which consists of various elements such as the adhesion protein Als3, enables C. albicans to colonize various surfaces and transition from a yeast form to a more invasive filamentous form. The extracellular matrix, composed of polysaccharides, proteins, and DNA, protects the cells within the biofilm from the action of antifungal therapy and enhances resistance to external influences.

The ALS3 gene is crucial in the biofilm formation of C. albicans. The Als3 protein it produces plays a role in initial adhesion and morphological transition, which are essential for forming a stable biofilm structure. Inhibiting ALS3 expression or mutating this gene can reduce C. albicans' ability to form a strong biofilm and decrease its virulence. Therefore, ALS3 is a potential target in the development of anti-biofilm therapies that could reduce the effectiveness of current antifungal treatments.

Furthermore, effective anti-biofilm therapy can reduce biofilm resistance to treatment by inhibiting

biofilm formation or disrupting the extracellular matrix. A combination approach involving both anti-biofilm and antifungal therapies is expected to improve drug penetration into the biofilm and enhance treatment outcomes. Given the importance of biofilms in increasing C. albicans resistance to treatment, therapeutic approaches targeting biofilm formation have the potential to improve the treatment of C. albicans infections and reduce the level of resistance to antifungal therapies.

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