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Candidiasis and Bacterial Interactions: An unexplored Aspect

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ABSTRACT

Under natural environmental settings or in the human body, the majority of microorganisms exist in complex polymicrobial biofilms adhered to abiotic and biotic surfaces. These microorganisms exhibit symbiotic, mutualistic, synergistic, or antagonistic relationships with other species during biofilm colonization and development. These polymicrobial interactions are heterogeneous, complex, and hard to control, thereby often yielding worse outcomes than monospecies infections.

Concerning fungi, Candida spp., in particular, Candida albicans is often detected with various bacterial species in oral biofilms. These Candida-bacterial interactions may induce the transition of C. albicans from commensal to pathobiont or dysbiotic organism. Consequently, Candida–bacterial interactions are largely associated with various oral diseases, including denture stomatitis, dental caries, periodontitis, peri-implantitis, endodontic infections, and oral cancer. Given the severity of oral diseases caused by cross-kingdom consortia that develop hard-to-remove and highly drug-resistant biofilms, fundamental research is warranted to strategically develop cost-effective and safe therapies to prevent and treat cross-kingdom interactions and subsequent biofilm development. While studies have shed some light, targeting fungal-involved polymicrobial biofilms has been limited. This mini-review outlines the key features of Candida-bacterial interactions and their impact on various oral diseases. In addition, current knowledge on therapeutic strategies to target Candida-bacterial polymicrobial biofilms is discussed.

Keywords: Candida albicans, Bacteria, Cross-kingdom biofilm, Oral diseases, Therapeutics

INTRODUCTION

In a wide variety of environments from natural settings to the human body, the majority of microorganisms exist in complex polymicrobial biofilms adhered to abiotic and biotic surfaces. During biofilm colonization and

development, microbes exhibit symbiotic, mutualistic, synergistic, or antagonistic relationships with other species. Those polymicrobial biofilms are often detrimental, causing food spoilage, industrial pipe fouling and corrosion, as well as human infectious diseases. Specifically, polymicrobial biofilms can cause various infections in a wide range of the human body, from the oral cavity to urinary tract These polymicrobial biofilms tend to be challenging to treat and often yield worse outcomes than monospecies infections by altering the sensitivity to antimicrobial agents.[1,2]

The gastrointestinal tract and the oral cavity are the representative human body parts that harbour a complex and diverse multitude of microorganisms, where they serve an essential role in local and systemic health. In particular, the oral cavity is a unique ecosystem that contains 600 to 1,000 bacterial species as well as more than 100 fungal species, colonizing soft and hard tissues either permanently or transiently. In health, commensal microbiota inhibits pathogen colonization while supplying the host with essential nutrients, maintaining a stable micro-ecosystem. However, disruptions of such commensal microbial communities from steady-state composition may result in the imbalance of host-microbiome interaction and illness. Although clinical evidence indicates that the coexistence of bacteria and fungus in the oral cavity may accelerate susceptibility to host infection, previous oral biofilm studies have largely focused on the development of bacterial biofilms (mostly monospecies), and the aspect of cross-kingdom interactions have been underexplored. However, recent mechanistic studies exhibit the role and importance of bacterial-fungal interactions during biofilm formation and development as well as their implication in oral health and disease states.[3,4]

Concerning fungi, Candida spp. are the most commonly detected fungal species in the oral cavity. Particularly, C. albicans is often found with various bacterial species in oral polymicrobial biofilms which may induce the transition of C. albicans from commensal to pathobiont or dysbiotic organism. In this cross-kingdom interaction, the cell wall of C. albicans, a critical structure for maintaining the cell shape and immunogenicity, plays an important role as the major point of contact between the fungus and bacteria. For example, hypha-specific adhesins, ALS (agglutinin-like sequence) group of cell wall glycoproteins (e.g., Als1 and Als3), are shown to mediate the cross-kingdom interaction of C. albicans with various bacteria commonly found in the oral cavity, such as Streptoccus gordonii, Streptococcus oralis. Porphyromonas gingivalis, Staphylococcus aureus, and Staphylococcus epidermidis. These Candida–bacterial interactions have been found to be associated with various oral diseases including dental caries, denture stomatitis, periodontitis, peri-implantitis, and oral cancer. Unfortunately, drug susceptibility studies revealed that it is challenging to eradicate those Candida-bacterial polymicrobial biofilm-induced diseases due to alterations of the efficacy of antibiotics by either fungal cells or bacteria and lack of targeting polymicrobial interactions. [5,6]

This mini-review aims to present the characteristics of Candida-bacterial interactions and their impact on polymicrobial biofilm formations in the context of various oral diseases. In addition, diverse therapeutic strategies to target Candida-bacterial polymicrobial biofilms are introduced.

Candida-bacterial biofilm-associated oral diseases

Bacterial colonization and biofilm formation on tooth surfaces or oral soft tissues are modulated by the type of species that initially bind and subsequent colonizers interacting with those. Candida-bacterial cross-kingdom interactions may also participate in those processes and affect biofilm development, thus contributing to the

severity of biofilm-associated oral diseases. There are numerous pieces of evidence showing that the association of C. albicans and various bacteria is implicated in diverse aspects of oral diseases, which are summarized in the following subsections. [7,8]

Dental caries

Dental caries, also known as tooth decay, is a representative biofilm- and diet-dependent oral disease. Among various fermentable sugars, sucrose is considered the most cariogenic due to its contribution to biofilm formation and development by serving as a substrate for the production of extracellular polysaccharides (EPS).While bacteria have been traditionally considered as a major component of the etiology of dental caries, many recent studies revealed that C. albicans are often detected from plaque biofilms, particularly in children with severe early childhood caries (ECC). Specifically, synergistic interaction between C. albicans and cariogenic bacterium Streptococcus mutans is heavily studied in vitro and in vivo in the context of dental caries. [9,10]

The consensus is that EPS produced by S. mutans plays an important role in mediating C. albicans-S. mutans cross-kingdom interaction, generating a virtuous cycle whereby it enhances C. albicans growth and metabolic activity, in turn, accelerating S. mutans growth and EPS production as well. This enhanced EPS production also facilitated the surface coating of C. albicans with EPS, established the alliance between C. albicans and S. mutans at an early stage of biofilm development, thereby outperforming S. gordonii in a 3-species mixed biofilm model. Interestingly, a more recent study showed that only C. albicans-S. mutans cross-kingdom biofilm matured and created an acidic microenvironment when cultured in human saliva, while S. mutans alone were not successful. In addition, a variety of other factors that involved in C. albicans-S. mutans interaction has been discussed. [11,12]

For example, one study revealed that the removal of extracellular DNA disrupted the initial stage of cross-kingdom biofilm formation. Other studies suggested that S. mutans antigen I/II, S. mutans collagen-binding proteins, deletion of the S. mutans delta subunit of RNA polymerase (RpoE), C. albicans-derived polysaccharide biofilm matrix, or the presence of alkaloid nicotine can boost the C. albicans-S. mutans cross-kingdom biofilm formation. Furthermore, the new critical role of C. albicans in inducing oral microbial dysbiosis that exacerbates the pathogenesis of root caries has been reported and the new cross-feeding mechanism between S. mutans and C. albicans has been suggested with the aid of multi-omics analyses. Other than C. albicans-S. mutans biofilms, cross-kingdom interactions of C. albicans with Actinomyces viscosus also significantly increased the cariogenic virulence of biofilm. Although some antagonistic interactions between C. albicans and S. mutans regarding inhibition of C. albicans hyphal formation have been reported it appears that most cross-kingdom interactions facilitate biofilm accumulation while increasing the acidogenicity of biofilm, amplifying the virulence of biofilms. [13,14]

Denture stomatitis

Denture stomatitis is an inflamed condition of the oral mucosa that is directly in contact with dentures. Although C. albicans has been extensively studied as the sole main etiological factor of denture stomatitis, recent studies revealed that cross-kingdom interactions between C. albicans and bacteria often prosper in

denture biofilms. For example, several studies reported frequent isolation of C. albicans with S. aureus or S. epidermidis from the oral mucous of patients wearing dental prostheses. In another study, Fusobacterium nucleatum as well as F. nucleatum subsp. animalis and vincentii were exclusively detected in high numbers with C. albicans from denture stomatitis patients. A recent profiling study demonstrated that a gram-positive anaerobe Scardovia showed a positive correlation with C. albicans from plaque formed inside of a denture, while three anaerobes (Leptotrichia, Lachnoanaerobaculum, and Moryella) showed a negative correlation. In addition, cooperative physical and metabolic processes among C. albicans, S. oralis, and Actinomyces oris were found to contribute to early biofilm formation on denture material from in vitro model. Similar to the findings from the dental caries study, the effect of nicotine is also appeared to increase the coaggregation of C. albicans and S. mutans in denture biofilm. [15,16]

Periodontitis

Periodontitis is caused by an imbalance between the microbiota and immune defense that results in the loss of soft-tissue seal around teeth, formation of periodontal pockets, and subsequent bone destruction. While various microorganisms have been known to be associated with the initiation and progression of the periodontitis, red complex, P. gingivalis, Tannerella forsythia, and Treponema denticola, as well as Aggregatibacter actinomycetemcomitans have been considered the most pathogenic bacteria involved in periodontitis. Lately, the role of yeast and its cross-kingdom interaction with various bacteria in periodontitis pathogenesis were discussed. Investigation of the associations of Candida and periodontopathic bacteria from seniors (≥ 60 years old) demonstrated that the surface area of inflamed periodontal tissue was significantly greater when Tannerella forsythia and Treponema denticola were detected together with C. albicans from patients. Also, several studies revealed various interaction mechanisms between C. albicans and P. gingivalis. For example, fungal cell adhesins Als3 and Mp65, aspartic proteases Sap6 and Sap9, and protein enolase appeared to mediate the direct physical contact with P. gingivalis. Particularly, C. albicans Als3 directly interacted with P. gingivalis InlJ, acting as an adhesin-receptor system for C. albicans-P. gingivalis association. Similarly, C. albicans surface mannoprotein Flo9 and F. nucleatum outer membrane protein RadD were involved in interspecies co-adherence. In other studies, it showed that virulence factors of P. gingivalis such as cysteine proteases and peptidylarginine deiminase enzymes played a crucial role in C. albicans-P. gingivalis association. As an environmental factor affecting C. albicans-P. gingivalis association, heme, an important iron source for both species, was shown to enhance the pathogenic potential of P. gingivalis while interacting with C. albicans. Such C. albicans-P. gingivalis association facilitated the invasion and infection of gingival tissue cells, and hampered wound closure. [17,18]

Peri-implantitis

Osseointegrated dental implants have become a clinical standard for replacing missing teeth. The inflammatory response of the gingival tissue around implants represents a growing challenge as many studies demonstrated a high incidence of peri-implant diseases after implantation. Such peri-implant diseases could lead to destructive failures, resulting in discomfort, painful and costly surgical replacement of failed implants, and the potential breakdown of overall oral health. The microbiota linked to dental implant failure has been shown to be associated with a higher prevalence of periodontal pathogens, such as P. gingivalis, Prevotella

intermedia, Fusobacterium spp, as well as gram-negative cocci, together with Candida spp. While the mechanistic investigation of cross-kingdom interaction between Candida and bacteria on peri-implantitis has been limited, there are some studies describing their implications. For example, one study demonstrated the mutualistic relationship between C. albicans and mitis group streptococci (i.e., Streptococcus mitis, Streptococcus sanguinis, S. oralis, and S. gordonii) promoted biofilm formation on titanium surfaces, resulting in increased tissue damage. Another study demonstrated similar findings that mutualistic C. albicans-S. gordonii cross-kingdom interactions enhanced biofilm formation and fostered a high level of resistance to combination therapy with antifungal and antibacterial drugs. In addition, there was a study aimed at evaluating the interaction between C. albicans and Streptococcus salivarius biofilms developed on titanium surfaces, under reduced oxygen levels. Unlike their antagonistic relationship observed in oral candidiasis models, the presence of S. salivarius did not affect fungus growth or C. albicans virulence in the context of peri-implant disease. Interestingly, virulence factors of C. albicans expressed in biofilms formed on titanium (i.e., expression of genes associated with adhesins and hydrolytic enzymes) significantly varied depending on associated bacterial species (e.g., S. sanguinis, S. mutans, and P. gingivalis). [19,20]

Oral cancer

Oral cancer is one of the most prevalent cancers which mainly occurs in the squamous . While various risk factors for oral cancer are known, including tobacco use, heavy alcohol consumption, and human papillomavirus infection, microbial infections also can contribute to its pathogenesis. In particular, C. albicans is considered one of the major microorganisms contributing to oral cancer development, potentially promoting carcinogenesis via several mechanisms. For instance, cross-kingdom interactions of C. albicans with oral bacteria A. naeslundii and S. mutans enhanced invasion of oral squamous cell carcinoma and increased the expression of cancerous inflammatory cytokines, which promoted oral carcinogenesis. Also, metabolites from C. albicans-S. aureus cross-kingdom biofilm promoted changes in proto-oncogenes and cell cycle gene expression in normal and neoplastic oral epithelial cell lines. It is worth noting that those cross-kingdom interactions are not only involved in the pathogenesis of oral cancer but also cause catastrophic complication. During cytotoxic chemotherapy, the dysbiotic state is often promoted, elevating the risk of oral candidiasis, which results in infectious complications that are a common cause of morbidity and mortality in cancer patients.This was proposed whereby the mutualistic relationships between C. albicans and Enterococcus faecalis facilitate their overgrowth, which augments mucosal barrier breach by releasing proteolytic enzymes and enhancing virulence gene expression by C. albicans.

Combined, cross-kingdom interactions between C. albicans and oral bacteria are widely associated with the virulence of various oral diseases. Thus, their mechanism of action should be further understood to successfully manage Candida-involved complex biofilm-associated oral diseases. Further investigations using clinically relevant ecological biofilm models combined with powerful analytical tools may progress our knowledge to the next level. [21,22]

Concluding Remarks

As summarized here, polymicrobial biofilms containing C. albicans and various pathogenic bacteria together are ubiquitously associated with a variety of oral diseases and have the potential to exacerbate diseases. Therefore,

it iterates the importance of expanding biofilm investigations from single-species systems to complex cross-kingdom relationships. Furthermore, it turned out that HIV-infected children are highly susceptible to C. albicans associated oral lesions, candidiasis, which is an important marker of immune suppression that may progress to more severe infections with other pathogens. Thus, more vigorous research efforts should be made to develop innovative antibiofilm therapeutics against fungal-associated polymicrobial biofilms. Although several approaches have been introduced to deal with cross-kingdom biofilms, the vast majority is relying on broad-spectrum antimicrobial activity that can kill both fungus and bacterium but lack targeting polymicrobial interactions. A recent binding mechanism-based non-microbicidal approach that intervenes in symbiotic C. albicans-S. mutans biofilm interaction suggests a new paradigm in treating cross-kingdom biofilms. Furthermore, it is worth noting that most of the current therapeutics has been mainly tested using in vitro model. A thorough assessment of the efficacy and safety of new therapeutics using an appropriate in vivo model should be accompanied for developing successful applications in the prevention and treatment of polymicrobial infections.

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