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Pathogenesis of Polymicrobial Biofilms

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Abstract: In polymicrobial biofilms a high level of interspecies interactions occur with often detrimental effect to the host. Many chronic infections are attributed to polymicrobial biofilms which tend to exhibit increased resistance to antimicrobial therapy. Yet despite the gravity of such infections, areas of study in polymicrobial diseases are in their infancy. Thus, much work is needed to promote a better understanding of emerging concepts in the biofilm development process such as interspecies communication and host immune response to microbial biofilms. The key challenges are to design effective therapeutic strategies to impede microbial colonization and prevent development of polymicrobial infections. Therefore, future research directions should focus on designing animal model systems to study *in vivo*-grown polymicrobial biofilms and infections. This review summarizes our limited knowledge about the nature of these complex communities and examines their role in disease, highlighting the challenges and novel approaches that are being pursued to combat polymicrobial biofilms and infections.

Keywords: Polymicrobial biofilms, interactions, *Candida albicans*, bacteria, infections.

INTRODUCTION

In most natural environments, microorganisms exist predominantly as multi species biofilms where intercellular interactions and communication are keys to survival [1-8]. Polymicrobial diseases, caused by combinations of viruses, bacteria, fungi, and parasites, are being recognized with increasing frequency [9]. The interactions between the various species in these mixed infections can be synergistic in that the presence of one microorganism generates a niche for other pathogenic microorganisms, predisposing the host to colonization or infection by a second organism [9]. In addition, the dense population structure in biofilms increases the opportunity of gene transfer between the species which can convert a previously avirulent commensal organism to a highly virulent pathogen [10]. This phenomenon of horizontal gene transfer is mediated mainly through bacterial plasmids, small, dispensable chromosomes which serve as vehicles that carry a considerable variety of genes. Some of these genes may be useful for the enhancement of survival under unfavorable conditions such as nutritional starvation and high cell density, two key characteristics of biofilm physiology [11-13]. Hence, plasmids including those that confer drug resistance and provide enzymes expand the nutritional ability of the cell and virulence determinants [13, 14]. The enhanced efficiency of gene transfer in biofilms induces enhanced stabilization of the biofilm structure but more importantly, also facilitates the spread of antibiotic resistance [10, 15]. Therefore, understanding how antibiotic resistance develops and is spread by mobile genetic elements is a pre-requisite to the design of intervention strategies intended to minimize the threat of bacterial infections. Alternatively, the presence of one microorganism may generate a niche in the host that suppresses the colonization of other microorganisms. This form of interaction is called "microbial interference" [9]. This review outlines our understanding of the nature of polymicrobial interactions in biofilm within the context of human disease with emphasis on novel prophylactic and therapeutic strategies targeting polymicrobial biofilms.

THE ART OF COMMUNICATION

In a biofilm environment, microbial species are highly interactive and employ a range of cell-to-cell communication or 'quorum sensing' systems [16-18]. This phenomenon for promoting collective behavior with in a population is important in ensuring survival and propagation by enhancing access to nutrients and niches, as well as providing protection [4, 5, 19]. Although much of what we understand today came from the study of single species biofilm, it is now clear that in the natural and clinical environments, most biofilms are likely to consist of consortia of species that influence each other in synergistic and antagonistic manners [4, 8, 20]. However, limited studies have specifically addressed interactions within multi species biofilms and particularly interactions between bacteria and fungi, which are often found together in a myriad of environments [16, 21-23]. Although the area of research exploring inter-kingdom interactions in biofilm is still in its infancy, there is increasing awareness of their clinical implications in the host particularly between the fungal pathogen *Candida albicans* and various bacterial species (for detailed description of some of these interactions *within the context of human disease*, the reader is referred to two recent reviews) [22, 23].

C. albicans is the major fungal pathogen of humans causing a variety of afflictions ranging from superficial mucosal diseases to deep seated mycoses [24-26]. Biofilm formation is a major virulence factor in the pathogenicity of *C. albicans* and *Candida* biofilms are difficult to eradicate

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due to their high resistance to antifungals [24, 26, 27]. Consequently, research into the pathogenicity of *C. albicans* has focused on the prevention of biofilm development and management of drug resistance [28]. A recent study examining the structure of biofilm formed by *C. albicans* and the bacterial pathogen *Staphylococcus aureus* as they co-exist revealed a unique architecture where *S. aureus* associated with the hyphae of *C. albicans*. Further characterization of this seemingly synergistic type of interaction at the molecular level demonstrated significant level of differential protein expression the result of the mixed-species biofilm mode of growth [29]. Interestingly, a number of these proteins were identified to be virulence factors in *S. aureus* indicating a process whereby *C. albicans* may enhance *S. aureus* pathogenesis [29]. These findings are of great significance as these two species are currently ranked as the second and third most commonly isolated bloodstream pathogens in hospitalized patients [24].

Another form of commensalism described in multi-species biofilms is "indirect pathogenicity" which was re-cognized during treatment failure of polymicrobial infections. This phenomenon describes an interactive association where one organism benefits while the other is not affected [30]. For example, in a mixed infection, an antibiotic-resistant microorganism of low intrinsic virulence protects an antibiotic-sensitive pathogen from eradication [30, 31]. Interestingly, a similar phenomenon was recently described for *S. aureus* and *C. albicans* where the co-existence of these human pathogens in a biofilm resulted in increased *S. aureus* resistance to vancomycin [32]. Alternatively, limited space and nutrients in biofilms can lead to competition between microorganisms resulting in antagonistic interactions, typified by one organism's direct, deleterious impact on another. An example of such antagonistic interaction is the one described between *Pseudomonas* and *Agrobacterium*, in which growth rate and motility impacted the fitness of each competitor [33]. However, a more clinically relevant antagonistic interaction is the one reported between *P. aeruginosa* and *C. albicans* where *P. aeruginosa* was shown to form dense biofilm on *C. albicans* hyphae and kill the fungus [34-36](Fig. (**1**) depicts the adherence of *S. aureus* and *P. aeruginosa* to *C. albicans* hyphae in biofilm).

THE ORAL MICROBIOME

The human mouth with its diverse niches and ample supply of nutrients is undoubtedly conducive for the unrestricted formation of natural microbial biofilms, such as those found on the tooth as dental plaque and oral mucosal tissue where a multitude of microbial species co-exist [31, 37]. Recent technological advances in metagenomic analyses have enhanced the identification and characterization of the vast microbial diversity colonizing the human body. The oral microbial communities are some of the most complex microbial floras in the human body, consisting of more than 700 different bacterial species [31, 38]. The analysis of the diversity and distributions of microorganisms in oral biofilm communities through microbiome studies, has allowed insight into the differences between the normal state of the oral microbiota and the alterations that are present during disease states [31, 38].

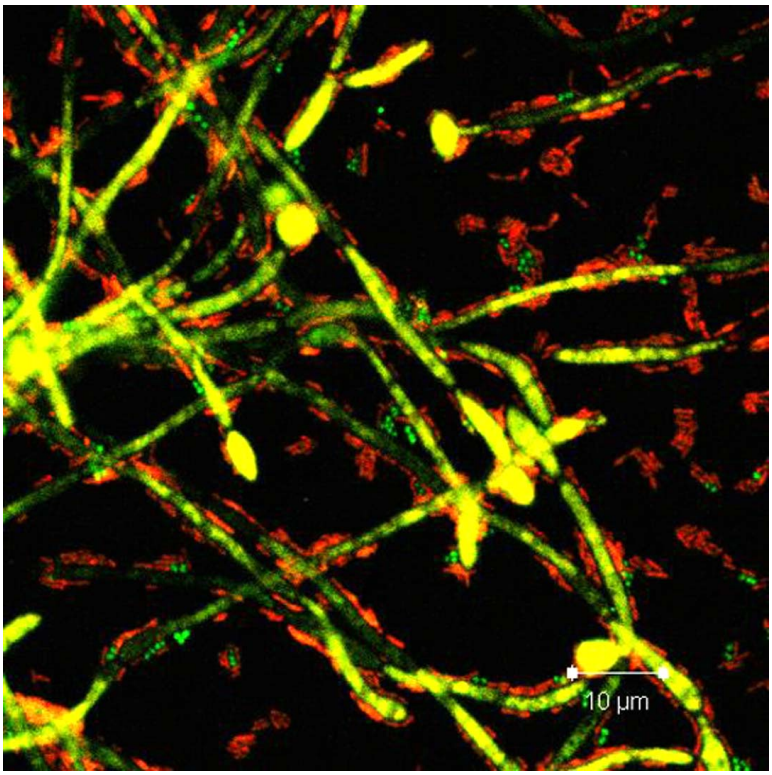

Fig. (1). Fluorescence *in situ* hybridization image of *C. albicans* and *S. aureus* mixed-species biofilm using fluoresce in and Tamra-labeled species-specific peptide nucleic acid probes demonstrating extensive adherence of *S. aureus* (green) and *P. aeruginosa* (red) to *C. albicans* hyphae (yellow).

In the oral cavity, *C. albicans* co-exist and form tight associations with various oral bacterial species. The range of intergeneric coaggregations occurring between *C. albicans* and oral species likely plays an important factor in *C. albicans* colonization where bacteria modulate fungal growth and biofilm formation [31]. *Streptococcus gordonii* specifically which is found on most oral cavity surfaces have been shown to interact with *C. albicans* to promote hyphal- and biofilm-formation [39]. The *C. albicans ALS* genes encoding a family of adhesins have been implicated in the adherence of *C. albicans* to surfaces including host tissue and bacteria. *ALS3*specifically, which encodes a hyphal cell wall-specific protein (Als3p) with adhesive properties was recently shown to be involved in the interactions of *C. albicans* with *S. gordonii*. Recently, a coaggregation study examining the interaction between, *S. gordonii* cells and *C. albicans* demonstrated that although the streptococci attached to the hyphae formed by *C. albicans* wild-type cells, they failed to attach to the hyphae produced by an *ALS3* deletion mutant strain [39]. In another study, the adhesive role of the Als3p was further demonstrated by blocking adhesion of *C. albicans* to buccal epithelial cells with immunoglobulin reactive against the Als3p N-terminal sequences [40].

The interactions between *C. albicans* and streptococci specifically, appear to be essentially synergistic where in addition to providing adhesion sites, the streptococci excrete lactate that can act as a carbon source for yeast growth [31, 41, 42]. More importantly, the most serious ramification of these fungal-bacterial interactions with clinical implications comes from findings demonstrating that the physical interactions between *C. albicans* and oral streptococci increased tolerance of the polymicrobial biofilm to anti-microbial agents and enhanced resilience to physical disruption [31]. Thus, when *Candida* infections arise, they often occur in association with bacteria. On the other hand, there is also strong evidence to suggest that components of the resident microflora present in the oral cavity and at other mucosal sites, perform to check *C. albicans* growth. This is why factors that perturb the normal microflora, such as antibiotic therapy or changes in hormonal or mucosal secretions, may encourage *C. albicans* overgrowth. A study evaluating the effect of eight aerobic and anaerobic oral commensal bacterial species on the growth and survival of *C. albicans* biofilms indicated that the quantitative and qualitative nature of the bacteria, modulate *C. albicans* biofilm formation in the oral cavity [43]. Similarly, a more recent study characterizing oral mucosal *C. albicans* biofilms concluded that *C. albicans* forms complex mucosal biofilms consisting of both commensal bacterial flora and host components [44]. Therefore, understanding the complex mechanisms by which *Candida* and oral bacteria co-colonize will assist in the development of new protocols to block adhesive reactions and eliminate *Candida* from biofilm-related oral infections such as denture stomatitis.

NOVEL STRATEGIES TO COMBAT POLYMICROBIAL BIOFILMS AND INFECTIONS

Many nosocomial infections involve microbial biofilms and persistence of chronic infections is attributed to the persistence of polymicrobial biofilms [9, 45]. In these situations, traditional therapies are generally targeted at individual causative agents without consideration for effect on a polymicrobial cause or on individual members of microbial communities. The standard treatment regimen employed for polymicrobial infections involves two or more antibiotics, referred to as combination therapies [9, 46]. The use of novel antibiotic combinations and antibiotic cycling may prolong the effectiveness of antibiotic therapies [47]. However, a careful attempt should be made to identify the causative microorganisms, as appropriate management of mixed infections requires the administration of anti-microbials that are effective against both components of the infection [46]. Significantly, the increasing emergence of drug resistance to commonly used antibiotics and antifungals has made the need for the identification of novel therapeutics and approaches critical. Therefore, development of effective strategies to control or prevent biofilm-associated infections requires a thorough understanding of the biofilm development process [48].

The medical community is recognizing the significance of polymicrobial diseases and the major types of microbial community interactions associated with human health and disease. Therefore, design of novel therapeutic strategies is just starting to take into account the polymicrobial cause of diseases and the repercussions on treatment and prevention [9]. Among the promising approaches to combat biofilm infections is the generation of surface modification of devices to reduce microbial attachment and biofilm development, as well as incorporation of antimicrobial agents to prevent colonization [49]. Similarly, several compounds and synthetic analogues have been used successfully to prevent biofilm formation such as farnesol, which was shown to effectively inhibit bacterial and fungal biofilm formation [50, 51]. Another option could be to coat biomaterial surfaces with organic molecules to prevent protein adsorption which may also inhibit biofilm formation [52]. Further, the biofilm matrix is composed of a variety of structural components, including DNA in addition to polysaccharides and proteins. Therefore, a promising strategy is the use of substances and enzymes (e. g. DNase and alginate lyase) able to disrupt and dissolve biofilms by attacking surface polysaccharides and the extracellular DNA which is critical for the early development of biofilms [53]. Along those lines, other innovative approaches consist of disrupting biofilms by exposing them to photodynamic substances [52]. Typically, biofilms must release and disperse cells into the environment in order to colonize new sites [54]. Therefore, biofilm dispersal is another promising area of research that may lead to the development of novel agents to promote biofilm cell detachment.

A new mechanism for novel prophylactic or therapeutic management of polymicrobial diseases targets another biofilm property, microbial interference, through the use of probiotics. The use of antibiotics and immunosuppressives often causes alterations in the composition of host microflora particularly in the oral cavity and the intestinal and urogenital tracts. Therefore, the introduction of beneficial microbial species may be a very attractive option to re-establish the microbial equilibrium and prevent disease [55]. Among the bacterial genera used in probiotic preparations are *Lactobacillus*, *Bifidobacterium*, *Escherichia*, *Enterococcus, Bacillus* and *Streptococcus* in addition to the fungal

species belonging to *Saccharomyces*. Through immune modulation pathogen displacement and creation of a niche less conducive to proliferation of pathogens and their virulence factors, probiotics were shown to be effective in varied clinical conditions such as antibiotic-associated diarrhea and *Helicobacter pylori* infections [55-57]. One good example is using lactobacilli to improve urogenital health in women.

Alternatively, the realization that a number of pathogens utilize the process of quorum sensing to establish a biofilm and control much of their virulence arsenal by means of extracellular signal molecules has identified the communication machinery as new drug targets. In fact, the process of quorum sensing was shown to be involved in the development of resistance to various antimicrobial treatments and immune modulation. Therefore, the use of quorum-sensing inhibitors that block communication may control biofilm formation, increase biofilm susceptibility to antibiotics as well as the susceptibility of the pathogens to host defenses [17, 58, 59]. Although quorum sensing antagonists hold great promise in fighting polymicrobial biofilms they should be viewed as blockers of pathogenicity rather than as antimicrobials. However, to define potential new strategies for impeding microbial colonization and development of polymicrobial disease will require a thorough understanding of the mechanisms of adhesion and inter-cellular signaling involved in mixed-species interactions.

Normal mucosal surfaces resist biofilm infections despite continual exposure to commensal and pathogenic microorganisms indicating that mucosal surfaces might possess an anti-biofilm defense. Yet, although much work has been done to address the role of biofilm mode of growth in antimicrobial resistance there have been very few studies addressing the role of biofilm resistance to the human immune system or the host response to polymicrobial biofilms. Therefore, much work is needed to promote a better understanding of host response, both innate and adaptive to microbial biofilms and future research should be directed towards studying the immunology of biofilms. Development of high throughput methods to identify host immunologic factors that are differentially expressed in biofilms may lead to the design of processes for enhancement of the role of innate immune factors in prevention or elimination of biofilms.

CONCLUSION AND FUTURE PERSPECTIVES

Although it is important to continue studies of the pathogenic properties of specific microbes, understanding the microbial communities and their interactions that drive sickness or health is key to combating polymicrobial diseases [31]. Yet despite their seriousness, expansive research into the area of polymicrobial infections have been lacking. A deeper understanding of the interactions involved in polymicrobial biofilms will provide a new perspective on the factors relevant to polymicrobial disease. The key challenges no ware to design strategies to prevent development of polymicrobial infections using emerging concepts such as interspecies interaction. To that end, new research directions should focus on designing animal model systems to study *in vivo*-grown polymicrobial biofilms and infections.

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