Bacteria and Biofilm

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Bacteria are fascinating microscopic cells that can live by themselves or be extremely social. Indeed, they can establish social interactions with other microorganisms to form highly organized communities known as biofilms. These consortia consist of adherent aggregates of microorganisms arranged within a matrix of a self-produced extracellular polymeric substance (EPS) composed of a mixture of polysaccharides, proteins and extracellular DNA. Biofilm-forming activity is a widespread bacterial feature found on natural and artificial surfaces. In natural environments, biofilms represent the preeminent lifestyle of bacteria which can have beneficial effects on plant growth promotion, organic compound degradation, including different aquatic ecosystems. Moreover, microbial biofilms have been found useful in food fermentation, the production of many bio-based materials, bioremediation, wastewater treatment and microbial fuel cells.

Keywords: Acinetobacter baumannii ; biofilm ; multidrug-resistant ; prevention ; treatment

1. Overview

Bacterial biofilms are a serious public-health problem worldwide. In recent years, the rates of antibiotic-resistant Gram-negative bacteria associated with biofilm-forming activity have increased worrisomely, particularly among healthcare-associated pathogens. *Acinetobacter baumannii* is a critically opportunistic pathogen, due to the high rates of antibiotic resistant strains causing healthcare-acquired infections (HAIs). The clinical isolates of *A. baumannii* can form biofilms on both biotic and abiotic surfaces; hospital settings and medical devices are the ideal environments for *A. baumannii* biofilms, thereby representing the main source of patient infections. However, the paucity of therapeutic options poses major concerns for human health infections caused by *A. baumannii* strains. The increasing number of multidrug-resistant *A. baumannii* biofilm-forming isolates in association with the limited number of biofilm-eradicating treatments intensify the need for effective antibiofilm approaches. This review discusses the mechanisms used by this opportunistic pathogen to form biofilms, describes their clinical impact, and summarizes the current and emerging treatment options available, both to prevent their formation and to disrupt preformed *A. baumannii* biofilms.

2. Biofilms

Bacteria are fascinating microscopic cells that can live by themselves or be extremely social. Indeed, they can establish social interactions with other microorganisms to form highly organized communities known as biofilms. These consortia consist of adherent aggregates of microorganisms arranged within a matrix of a self-produced extracellular polymeric substance (EPS) composed of a mixture of polysaccharides, proteins and extracellular DNA [1].

Biofilm-forming activity is a widespread bacterial feature found on natural and artificial surfaces [2]. In natural environments, biofilms represent the preeminent lifestyle of bacteria which can have beneficial effects on plant growth promotion [3], organic compound degradation [1], including different aquatic ecosystems [4][5]. Moreover, microbial biofilms have been found useful in food fermentation, the production of many bio-based materials, bioremediation, wastewater treatment and microbial fuel cells [6][7][8][9][10].

Despite these beneficial and useful roles, biofilms also represent a significant threat for public health, being responsible for persistent infections with relevant economic and health impacts. In fact, biofilms account for 65% of microbial diseases and about 80% of chronic infections, associated to both medical devices and biotic surfaces [11]. Indeed, biofilms can occur on any type of medical device surface, such as catheters, breast implants, contact lenses, heart valves, pacemakers and defibrillators, ventricular shunts, and joint prostheses [12]. On the other hand, non-device-associated biofilms are represented by periodontitis, osteomyelitis, otitis media, biliary tract infection, and endocarditis [13]. Bacterial biofilm infections are very difficult to treat because these social interactions are highly resistant to antibiotic treatment and immune responses. The main pathogenic biofilm producers include the Gram-positive *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus viridans* and the Gram-negative *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. Among them, some

belong to the group of most concerning antibiotic-resistant bacterial pathogens, named ESKAPEE (*Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, *Enterobacter* spp. and *E. coli*).

The poor susceptibility of biofilms to host immune defenses and antibiotics can be due to the barrier effect of the EPS, but also to substantial changes in gene expression that result in phenotypic, metabolic, and growth changes, including the genes involved in antibiotic resistance [14]. Although acting as a barrier, the EPS has a functional architecture to ensure the delivery of nutrients to all the cells embedded in the biofilm [15]. The architecture of biofilms depends on several factors, including the EPS composition, bacterial motility, intercellular communication, and environmental conditions. All these variables affect the development, shape and amount of biofilms that individual species can produce. In addition, despite several common strategies, Gram-negative bacteria have evolved unique features in biofilm formation because of their structural differences, compared to Gram-positive bacteria. In fact, Gram-negative bacteria are didermic cells in that their cell envelope contains an inner (IM) and an outer membrane (OM) and a periplasmic space in between. The peculiarities of their cell envelope and extracellular appendages play critical roles in biofilm formation.

A. baumannii has emerged as one of the most threatening members of the ESKAPEE group for having intrinsically or easily acquiring multiple antibiotic-resistance mechanisms and for its long-lasting persistence in the environment. Survival even in dried environmental conditions is tightly connected with its ability to form biofilm. This feature in conjunction with the overuse of antibiotics has allowed *A. baumannii* to perfectly adapt to healthcare environments, thereby representing a source of spread of this opportunistic pathogen. Therefore, the general aim of this review is to highlight improvements in the understanding of the biofilm formed by *A. baumannii*. The World Health Organization (WHO) listed this microorganism as a life-threatening bacterium due to its resistance to most, if not all, existing therapeutic treatments (https://www.who.int/news/item/ accessed on 22 June 2017). Specifically, the mechanisms underlying biofilm formation, the burden of antibiotic resistance, the clinical impact of the biofilm-related infections, and the therapeutic strategies for their treatment and prevention, are discussed.

3. Conclusions

Biofilms are considered to dominate and shape life on Earth. Interestingly, the human gut, skin and oral microbiota comprise bacterial cells organized in complex biofilms. However, biofilms produced by pathogens such as *A. baumannii* in those environments in which human beings are most vulnerable (e.g., hospitals and communities) represent an increasing threat to our health. For this reason, studies of this microorganism have been boosted in the last decade. Some typical features have emerged; an increasing body of evidence highlights the high degree of heterogeneity among healthcare-associated isolates differentiating the ones tightly connected with the host (patients) vs. those strains residing in hospital settings. We are learning that *A. baumannii* is a master of adaptation. It easily adapts to whatever stimuli it perceives from the environment, with the ability to resist desiccation, antibiotics, disinfectants, and the host's immune defenses. In the last decades, *A. baumannii* MDR strains have thrived in healthcare environments and the biofilm-forming activity is a successful strategy that *A. baumannii* uses for survival and persistence. Several promising approaches are under investigation to prevent biofilm formation within hospital settings, including the downregulation of biofilm-associated genes, inhibition of QS signals, EPS production, efflux pumps as well as new antibiotics and antibiofilm antibodies. In addition, although once established, *A. baumannii* biofilms are very difficult to treat; ongoing new strategies are aimed at disrupting preformed biofilm, such as the use of peptides, photodynamic inactivation, phage-based therapy, and potentiation of antibiotics. Currently, as biofilms are such a public health issue, well-trained health care workers should be more closely involved in the detection, management, and treatment of healthcare-associated biofilms. In the near future, it would be highly desirable to see a synergic effort from scientists, clinicians, and pharmaceutical companies to effectively eradicate biofilms.

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