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New frontiers for anti-biofilm drug development

Suzana M. Ribeiro [a,b], Mário R. Felício [c], Esther Vilas Boas [a], Sónia Gonçalves [c], Fabrício F. Costa [b], Ramar Perumal Samy [d], Nuno C. Santos [c], Octávio L. Franco [a,b,*]

[a] S-Inova Biotech, Pos Graduação em Biotecnologia, Universidade Católica Dom Bosco, Campo Grande, MS, Brazil
[b] Centro de Análises Proteômicas e Bioquímicas, Pós-graduação em Ciências Genômicas e Biotecnologia, Universidade Católica de Brasília, Brasília, DF, Brazil
[c] Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal
[d] Department of Microbiology and Immunology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

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ABSTRACT

Pathogenic microbial biofilm, a consortium of microbial cells protected by a self-produced polymer matrix, is considered a worldwide challenge due to the inherent antibiotic resistance conferred by its lifestyle. Living, as it does, in a community of microbial organisms in a clinical situation, makes it responsible for severe and dangerous cases of infection. Combating this organisation of cells usually requires high antibiotic doses for a prolonged time, and these approaches often fail, contributing to infection persistence. In addition to therapeutic limitations, biofilms can be a source of infections when they grow in medical devices. The challenge imposed by biofilms has mobilised researchers in the entire world to prospect or develop alternatives to control biofilms. In this context, this review summarises the new frontiers that could be used in clinical circumstances in order to prevent or eliminate pathogenic biofilms.

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1. Introduction

Treatment of infections has become a worldwide challenge due to the development of antibiotic resistance among microorganisms, especially when resistance at cellular levels and at community level occur together (Fig. 1). Cellular antibiotic resistance, also referred to as conventional resistance, may occur when antibiotic targets are modified, microbial enzymes inactivate antibiotics and microorganisms prevent or reduce the antibiotic accumulation in their cells (Blair et al., 2015). Resistance observed in a community of microorganisms, known as biofilms, takes place when microbial cells aggregate (Bjarnsholt et al., 2013; G. Zhou et al., 2015; L. Zhou et al., 2015). Resistance to antibiotics can be even higher when single cells that present conventional resistance form a biofilm.

Biofilms consist of one or more microbial species, which can be in different metabolic states, encased in a self-produced biopolymer matrix composed by proteins, polysaccharides and DNA (Bjarnsholt

Abbreviations: AMPs, antimicrobial peptide; FDA, United States Food and Drug Administration; NPs, nanoparticles.

* Corresponding author at: Universidade Católica de Brasília, Pos-Graduação em Ciências Genômicas e Biotecnologia, Centro de Análises Proteômicas e Bioquímicas, SGAN 916, Av. W5, Módulo C, sala 219, Brasília, DF CEP 70790–160, Brazil. Tel.: +55 61 34487167, +55 61 34487220; fax: +55 61 33474797.
E-mail address: ocfranco@gmail.com (O.L. Franco).

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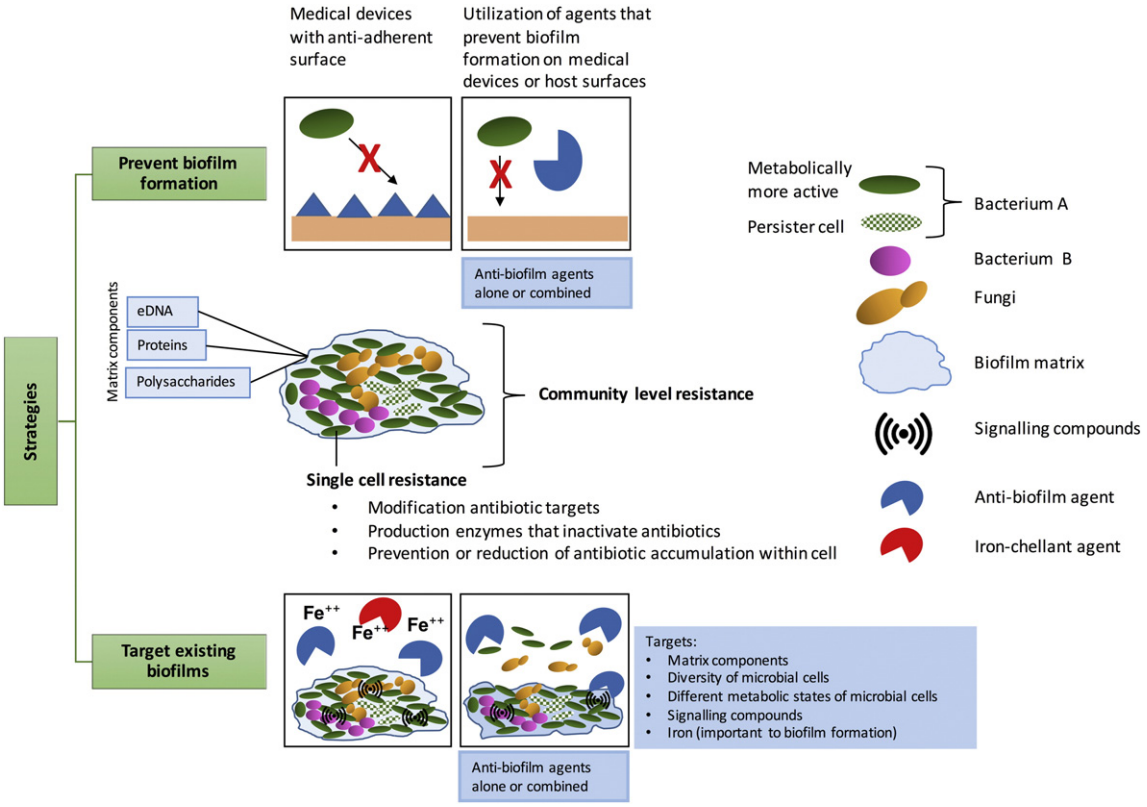

Fig. 1. Schematic diagram showing a common biofilm profile, mechanisms of antibiotic resistance and possible anti-biofilm strategies.

et al., 2013) (Fig. 1). In clinical environments, this resistant profile can develop on human body tissue surfaces and medical devices (Romling et al., 2014). Antibiotic therapies against biofilms usually require the use of high doses for prolonged time, and they often fail to combat persistent infections associated with biofilms (Beloin et al., 2014). Besides, most available antibiotics have been developed to target planktonic microbial cells, leading to a big gap in the biofilm field.

Potential candidates may act in preventing, disrupting, weakening or killing the microbial community within a biofilm (Bjarnsholt et al., 2013). In the prevention, anti-biofilm compounds may kill the planktonic cell or block biofilm formation by living cells. In the disrupting process, anti-biofilm compounds may destabilise the matrix, making the microbial cells within the biofilms susceptible to antimicrobial and/or host defense mechanisms (Bjarnsholt et al., 2013). In the weakening approach, anti-biofilm agents may neutralise virulence factors or affect processes involved in biofilm formation, such as quorum sensing. In the killing process, anti-biofilm compounds may present a bactericidal action upon microbial cells from biofilm (Bjarnsholt et al., 2013).

In this review, we present different approaches that have been proposed to decrease biofilm formation (Fig. 1). Attempts to fight against these cellular organisations include drug repurposing, peptides and peptide-based composites, a combination of different compounds aiming to target different aspects of biofilm, development of nanomaterials to combat and/or improve the diagnostic biofilm infections and the development of medical devices made with anti-adherent material or functionalised with anti-biofilm compounds.

2. The challenge of resistant bacterial biofilms

Currently, bacterial pathogenic biofilms are a remarkable challenge in the medical settings. Biofilm-associated infections are difficult to treat, usually requiring high antibiotic doses (Wu et al., 2015). The concentration of antibiotics to eradicate this bacterial organisation is commonly higher than that used to inhibit or kill its planktonic counterpart. This resistant life style can overcome host defenses and antibiotic therapies, contributing to the increase of morbidity and mortality in infected patients and consequently increasing hospital costs (Romling et al., 2014).

Pathogenic biofilms are normally associated with a number of persistent and chronic infections such as otitis media (Qureishi et al., 2014), periodontal disease (Jhajharia et al., 2015), non-healing wounds and skin infections (Cooper et al., 2014), lung infections in patients with cystic fibrosis (Ciofu et al., 2015), chronic rhinosinusitis (Madeo & Frieri, 2013) and urogenital infections (Zhao et al., 2013). The success of biofilm development in host tissues could be related to immune defense failure in preventing microbial colonisation or in the elimination of existing biofilms. Otherwise, the prolonged and/or exacerbated response of the host defense against biofilms can damage the host tissue and the neighbourhood, where this microbial community develops, and this may progressively impact the life quality of patients with chronic infections (Beikler & Flemmig, 2011; Zhao et al., 2013; Helwig et al., 2014; Cantin et al., 2015).

Some groups of people present a high risk of developing biofilm infections due to underlying diseases such as diabetes (Mottola et al., 2015) and cystic fibrosis (Ciofu et al., 2015). They become more susceptible to the development of biofilm due to the poor ability of their body to limit biofilm formation. For example, impaired healing of wounds in diabetics may facilitate bacterial development of pathogenic biofilms (Hurlow et al., 2015). Patients with cystic fibrosis have difficulty in coughing up the sputum, making the lung an ideal place for the establishment of biofilm infections (Gupta et al., 2015). Other conditions can facilitate biofilm development, including the exposure of internal body parts to medical devices, such as implants and catheters (Gupta et al., 2015), and poor oral hygiene (Marsh, 2010).

Moreover, biofilms can cause problems beyond the site where the biofilm resides, due to the dispersion of bacterial cells to other parts of the body or through the production of compounds that can trigger other diseases – apart from infections – such as cancer (Johnson et al.,