



Biofilm-associated proteins as potential drug targets

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Abstract

Biofilm-associated proteins (BAPs) are important in the development and resilience of biofilms, which are intricate populations of microbes protected by extracellular matrix. All members of the BAP family are known to possess common characteristics such as high molecular weight and a signal sequence for extracellular secretion. It has been shown that BAPs are directly linked to the pathogenicity of many bacteria. This mini review highlights several potential strategies to target BAPs for drug development.

Key words: Biofilm, Proteins, Drug target, Essential, Non-host homologous

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1. Introduction

Biofilms are commonly found in various environments, including medical devices, industrial settings, and natural ecosystems. They are of particular concern in the context of human health because biofilm forming bacteria are often more resistant to antibiotics and immune system defences than their planktonic counterparts. Biofilm formation has become an important survival mode of microbes during antimicrobial treatments (Zakaria *et al.*, 2023). This resistance poses a significant challenge in treating biofilm-related infections. Biofilm-associated proteins (BAPs) play a significant role in the formation and stability of biofilms, which are complex communities of microorganisms encased in a protective extracellular matrix. All members of the BAP family share the following characteristics: (i) a high molecular weight; (ii) a signal sequence for extracellular secretion; and (iii) a core domain of repeats, whose number varies among different isolates (Cucarella *et al.*, 2004).

One of the distinctive features of BAPs is their non-host homologous nature (Table 1). This means that these proteins do not have counterparts or homologous equivalents in the host organisms or tissues with which they interact. BAPs typically have unique protein sequences that distinguish them from host proteins. These sequences may contain specific domains or motifs that enable their functions within biofilms, such as adhesion domains or matrix-binding domains. BAPs are specifically produced by microorganisms, including bacteria, fungi, and algae, for their biofilm-related functions. This specificity ensures that BAPs do not have functional homologs in host tissues, reducing the risk of unintended interactions. BAPs are adapted to the biofilm environment and perform specialized roles within biofilms. These roles may include mediating cell-cell interactions, participating in quorum sensing, and contributing to the maintenance of the extracellular matrix. BAPs often contain specific domains and motifs that govern their interactions with surfaces, other biofilm components, and microorganisms. Examples include fibronectin-binding domains, lectin-like domains, and carbohydrate-binding motifs (Henderson and Geoghegan, 2023).

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Entry	Bacterial species	BLASTp (Selected taxonomy)	Result
Q79LN3	<i>Staphylococcus aureus</i>	Homo sapiens	No significant similarity found.
Q4ZHU1	<i>Staphylococcus epidermidis</i>	Homo sapiens	No significant similarity found.
Q4ZHU2	<i>Staphylococcus simulans</i>	Homo sapiens	No significant similarity found.

Understanding the role of BAPs is crucial in developing effective strategies to target biofilms as potential drug targets. These proteins possess various characteristics, including essential metabolic functions within biofilms and the distinction of being non-host homologous (Othman and Yahya, 2019). Although many antibiotics, disinfectants, antifungals and natural products have been demonstrated to possess antibiofilm potential, their effects on expression of the BAPs remain not well investigated (Isa *et al.*, 2022; Kamaruzzaman *et al.*, 2022; Amran *et al.*, 2023; Johari *et al.*, 2023). In this mini review, we explore the multifaceted roles of BAPs in biofilm formation, their implications in infections, and their potential as targets for therapeutic intervention.

2. Biofilm formation and extracellular matrix

Biofilms are intricate structures formed by various microorganisms, including bacteria, fungi, and algae. The extracellular matrix of biofilms is primarily composed of polysaccharides, DNA, and proteins (Yaacob *et al.*, 2021). Among these components, BAPs play a vital role in several key aspects of biofilm development. BAPs facilitate the initial attachment of microorganisms to surfaces. These proteins contain adhesive domains that interact with specific receptors on host tissues or abiotic surfaces. For example, in *Staphylococcus aureus*, the biofilm-associated protein Bap (encoded by the *icaADBC* cluster) is involved in adhesion to host tissues, promoting biofilm formation (Cucarella *et al.*, 2004). BAPs contribute to the structural integrity of the extracellular matrix. They can cross-link with other matrix components, such as polysaccharides and DNA, creating a robust and protective environment for embedded microorganisms. This matrix serves as a barrier against antibiotics and immune system attacks. Once formed, biofilms require stability to persist on surfaces. BAPs also help maintaining the structural integrity of the biofilm, preventing detachment and dispersion of microorganisms. This stability enhances the resilience of biofilms against antimicrobial agents.

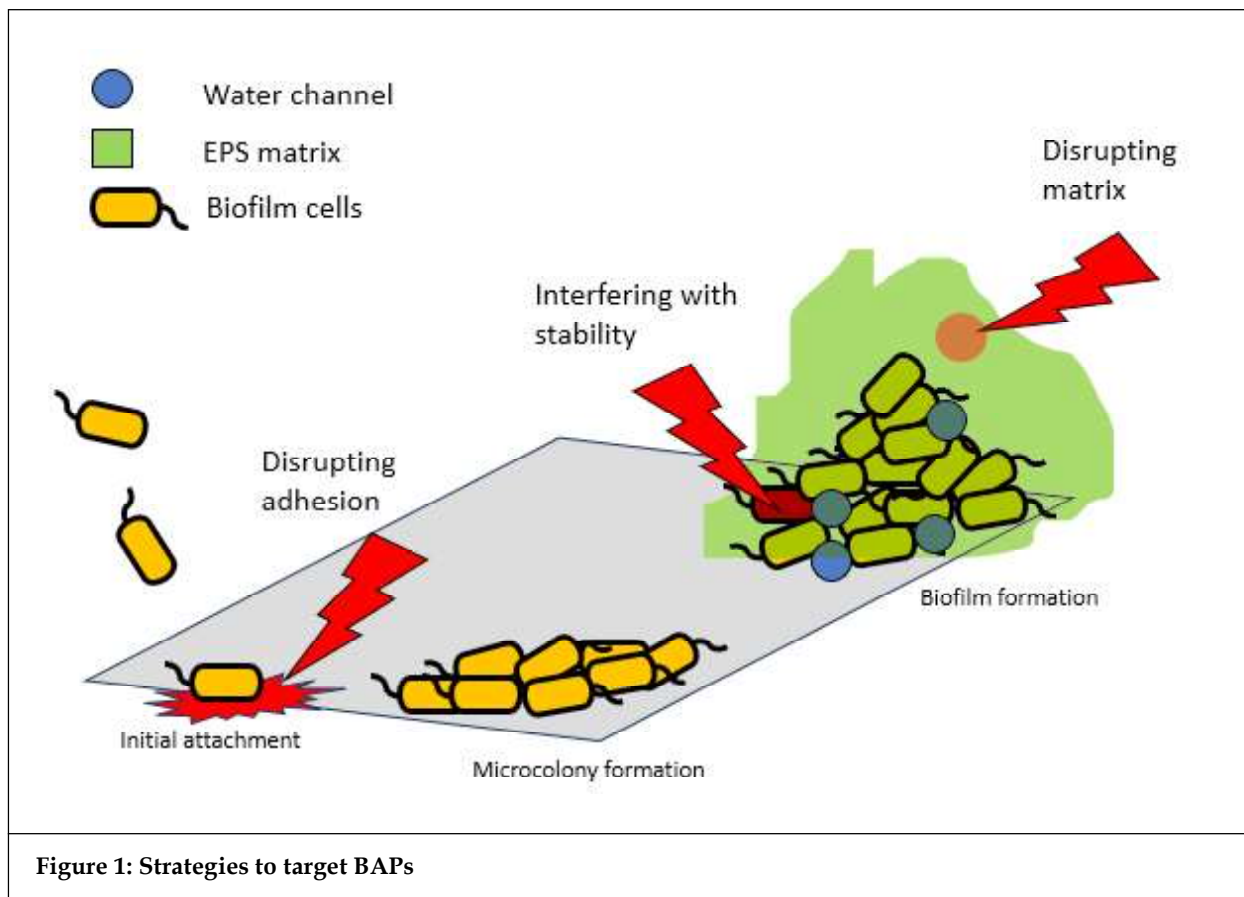
3. Implications in infection

BAPs are directly linked to the pathogenicity of many bacteria (Mohamed *et al.*, 2023). Understanding their role in infections is crucial for developing targeted therapies. Biofilm formation is often associated with chronic infections, such as those caused by *Pseudomonas aeruginosa* in cystic fibrosis patients or *Staphylococcus aureus* in implant-related infections. BAPs are integral to the persistence of these infections, as the biofilm matrix protects bacteria from host defences and antibiotics. Medical devices, such as catheters and prosthetic implants, can become sites of biofilm formation (Di Domenico *et al.*, 2022). BAPs promote the colonization of these devices by pathogenic bacteria, leading to device-related infections. Targeting these proteins could help prevent such infections. BAPs is known to contribute to antibiotic resistance by physically shielding bacteria within the biofilm matrix. This resistance poses a significant challenge in treating infections associated with biofilms. Inhibiting these proteins could potentially make biofilm bacteria more susceptible to antibiotics.

4. Biofilm-associated proteins as potential drug targets

The role of BAPs in biofilm formation and infection pathogenesis makes them attractive targets for therapeutic intervention. Their essentiality is apparent in cellular adhesion, matrix formation, and biofilm stabilization (Cucarella *et al.*, 2004). Figure 1 summarizes how these proteins can be targeted for drug development.

Inhibiting the adhesive properties of BAPs can prevent the initial attachment of microorganisms to surfaces. This could be achieved through the development of small molecules or peptides that block the binding domains of these proteins (Parrino *et al.*, 2019). By preventing adhesion, the formation of biofilms can be impeded, reducing the risk of infection. Targeting the interactions between biofilm-associated proteins and other matrix components can destabilize the biofilm structure. Enzymes or compounds that degrade polysaccharides, DNA, or protein components of the matrix may weaken biofilms, making them more vulnerable to treatments.



Biofilm-associated proteins are essential for maintaining the stability of mature biofilms. The use of inhibitors, such as cinnamaldehyde, that disrupt the function of these proteins could lead to the detachment and dispersion of biofilm microorganisms (Topa *et al.*, 2020). This could enhance the effectiveness of antibiotics and host immune responses against biofilm infections. Combining therapies that target BAPs with conventional antibiotics or antimicrobial agents may be a promising approach. Such combination therapies can potentially overcome the antibiotic resistance observed in biofilm infections.

5. Challenges and future directions

While targeting BAPs holds promise in combating biofilm-related infections, several challenges and considerations must be addressed. Developing drugs that overcome the increase in antibiotic-resistant bacteria and selectively target biofilm-associated proteins without affecting essential host proteins is a challenge (Abd Rashid *et al.*, 2022; Elfadil *et al.*, 2022; Sigurdsson, 2022). Specificity is crucial to minimize potential side effects. Bacteria may develop resistance to therapies that target BAPs. Continuous monitoring and adaptation of treatment strategies may be necessary. Biofilms are heterogeneous structures (Yaacob *et al.*, 2021), and the effectiveness of therapies can vary within the same biofilm. Understanding this heterogeneity is essential for developing effective treatments. Developing efficient delivery methods for biofilm-targeting therapies, especially for biofilms in hard-to-reach areas of the body, is crucial. Translating biofilm-targeting therapies from preclinical studies to clinical trials is a complex process that requires rigorous testing for safety and efficacy.

6. Conclusion

BAPs play pivotal roles in biofilm formation and infection pathogenesis. Understanding these roles offers opportunities to develop novel strategies to combat biofilm-related infections. By targeting these proteins, researchers aim to disrupt adhesion, destabilize the biofilm matrix, and improve the effectiveness of treatments. However, addressing challenges related to specificity, resistance, and biofilm heterogeneity is essential in advancing these potential drug targets from laboratory research to clinical practice. The development of therapies targeting BAPs has the potential to revolutionize the treatment of biofilm-related infections, providing hope for better outcomes in patients affected by these challenging infections.

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