Table 1: Non-host homologous BAPs. Protein sequence similarity search is performed using BLASTp program

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

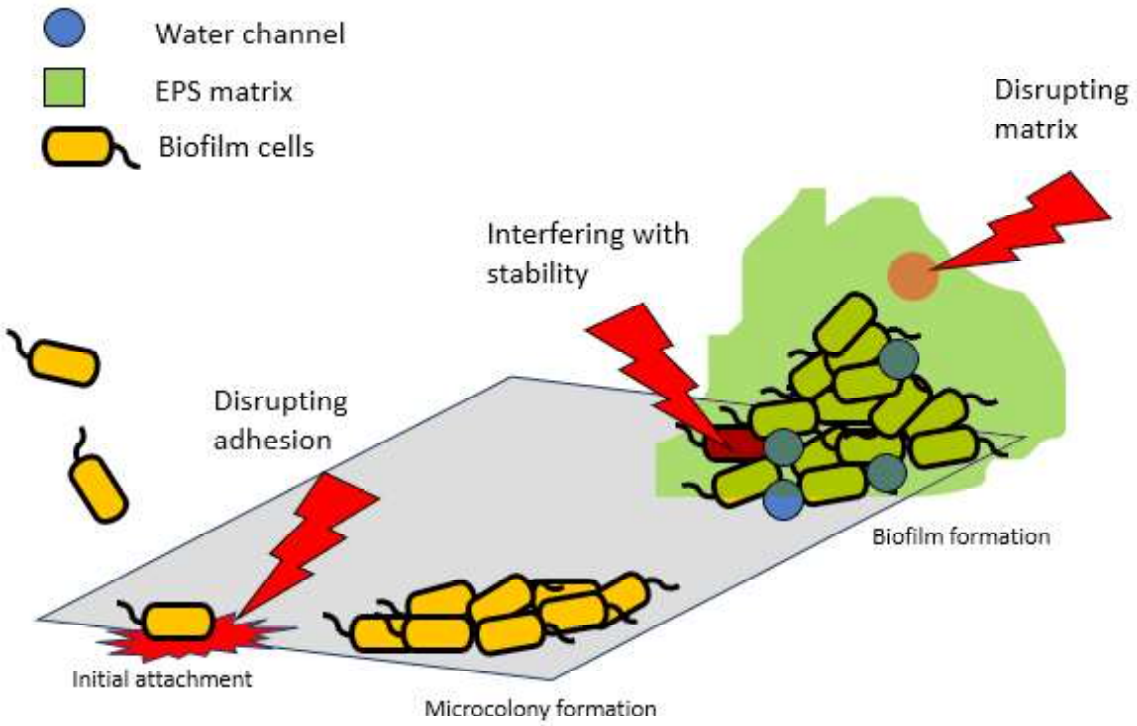

Figure 1: Strategies to target BAPs

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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