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Cell-wall-anchored proteins affect invasive host colonization and biofilm formation in *Staphylococcus aureus*

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ABSTRACT

As a major human and animal pathogen, *Staphylococcus aureus* can attach to medical implants (abiotic surface) or host tissues (biotic surface), and further establish robust biofilms which enhances resistance and persistence to host immune system and antibiotics. Cell-wall-anchored proteins (CWAPs) covalently link to peptidoglycan, and largely facilitate the colonization of *S. aureus* on various surfaces (including adhesion and biofilm formation) and invasion into host cells (including adhesion, immune evasion, iron acquisition and biofilm formation). During biofilm formation, CWAPs function in adhesion, aggregation, collagen-like fiber network formation, and consortia formation. In this review, we firstly focus on the structural features of CWAPs, including their intracellular function and interactions with host cells, as well as the functions and ligand binding of CWAPs in different stages of *S. aureus* biofilm formation. Then, the roles of CWAPs in different biofilm processes with regards in development of therapeutic approaches are clarified, followed by the association between CWAPs genes and clonal lineages. By touching upon these aspects, we hope to provide comprehensive knowledge and clearer understanding on the CWAPs of *S. aureus* and their roles in biofilm formation, which may further aid in prevention and treatment infection and vaccine development.

1. Introduction

As a major human and animal pathogen, *Staphylococcus aureus* can attach to medical implants (abiotic surface) or host tissues (biotic surface), and further establish robust biofilms which enhances resistance and persistence to host immune system and antibiotics (Ribeiro et al., 2012). Biofilms are bacterial aggregates encapsulated in an extracellular matrix composed of proteins, DNA and polysaccharides. Biofilm formation includes three stages: initial adhesion, biofilm accumulation, maturation and diffusion, and this complex process is largely influenced by production of polysaccharides and surface proteins (Speziale et al., 2014; Arciola et al., 2015; Balducci et al., 2023). In *S. aureus*,

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polysaccharides within the extracellular polymeric substance (EPS) facilitate the colonization of planktonic cells on biotic or abiotic surfaces, contributing to bacterial aggregation (Balducci et al., 2023).

As the major type of surface proteins, cell-wall-anchored (CWA) proteins (CWAPs) covalently link to peptidoglycan, and largely facilitate the colonization of *S. aureus* on various surfaces (including adhesion and biofilm formation) and invasion into host cells (including adhesion, immune evasion, iron acquisition and biofilm formation) (O'Brien et al., 2002; Grigg et al., 2010; Sharp et al., 2012; Foster et al., 2014; Geoghegan and Foster, 2017). Anchoring of these surface proteins to the cell wall is essentially required for CWAPs to be functional, and this process is mediated by sorting enzymes sortase A (SrtA) and sortase B (SrtB) which recognize the canonical Leu-Pro-*X*-Thr-Gly (LPXTG; with X representing any amino acid) and Asn-Pro-Gln-Thr-Asn (NPQTN) motifs, respectively (Mazmanian et al., 2001, 2002). Functions of sorting enzymes differ among the growth conditions of *S. aureus* cells, due to the fact that one structural domain is able to bind different ligands, and different structural domains recognize ligands with multiple functions (Deivanayagam et al., 2002; Ganesh et al., 2008; Kang et al., 2013; Thammavongsa et al., 2013; Shi et al., 2021). CWAPs possess multiple structural domains (signal peptides, N-terminal domains, repetitive sequences, and C-terminal anchoring domains), which could be recognized by various molecules.

During biofilm formation, CWAPs function in adhesion, aggregation, collagen-like fiber network formation, and consortia formation. Among CWAPs, binding of ClfA to fibrinogen and FnBP to integrins contributes microbial adhesion and aggregation (McDevitt et al., 1997; Ganesh et al., 2008), maturation (Josse et al., 2017). Bap binds to other proteins (Gp96, fibronectin, loricrin) and molecules (Ca^{2+}, Zn^{2+}) and thus plays a role in biofilm proliferation and maturation. Other CWAPs interact with microorganisms (virus, *Streptococcus oralis*, *Streptococcus mutans*, etc) to form biofilm consortia and enhance biofilm stability, or bind to other cell wall components including lipoteichoic acid (LTA) and wall phosphatidic acid (WTA) during biofilm formation. Gram-positive bacteria produce lipoteichoic acid polymers, and thus LTA affects bacterial surface properties (Xia et al., 2010), which is critically important for *S. aureus* biofilm formation on hydrophobic polystyrene surfaces (Fedtke et al., 2007). WTA, another important cell wall component, affects the expression of CWAPs genes which regulates biofilm formation (Zhu et al., 2018).

In this review, we firstly focus on the structural features of CWAPs, including their intracellular function and interactions with host cells, as well as the functions and ligand binding of CWAPs in different stages of *S. aureus* biofilm formation. Then, the roles of CWAPs in different biofilm processes with regards in development of therapeutic approaches are clarified, followed by the association between CWAPs genes and clonal lineages. By touching upon these aspects, we hope to provide comprehensive knowledge and clearer understanding on the CWAPs of *S. aureus* and their roles in biofilm formation, which may further aid in prevention and treatment infection and vaccine development.

2. CWAPs architecture and function

Up to date, over 20 distinct CWAPs have been identified in *S. aureus*, and their roles are categorized into five groups based on the presence of motifs, as below.

2.1. Microbial surface components recognizing adhesive matrix molecules (MSCRAMM) family

Microbial adhesion to host tissues is mediated by cell surface proteins specifically binding with extracellular matrix components, such as fibronectin, fibrinogen, collagen, and other ligands, and these surface proteins are designated as Microbial surface components recognizing adhesive matrix molecules (MSCRAMM) (Patti et al., 1994). Proteins in this family possess an A structural domain which contains N1, N2, and N3 sub-structural domains (Fig. 1). Through Dock, Lock, and Latch (DLL) or collagen hug (CH) mechanisms, MSCRAMM proteins bind to ligands on cell surface, contributing to further biofilm formation and immune evasion.

The MSCRAMM family includes ClfA, ClfB, FnbpA, FnbpB, Sdr, and Cna, etc. ClfA binds to C-terminal residue of fibrinogen γ-chain through DLL, while ClfB binds to fibrinogen α-chain (Deivanayagam et al., 2002; Ganesh et al., 2008; Walsh et al., 2008). As previously reported, adherence of *S. aureus* to squamous cells was influenced by ClfB, IsdA, SdrC, and SdrD (Corrigan et al., 2009), while interaction between SdrD and desmoglein 1 was crucial for adhesion to host cells (Askarian et al., 2016). Also, binding of MSCRAMM proteins to multiple ligands enables immune escape in the host. For examples, ClfB bound to complement factor I and H, and subdomains N2 and N3 of FnbpA, FnbpB, and ClfA bound to complement factor H, which mediated C3b degradation and further led to *S. aureus* immune escape (Hair et al., 2010; Mao et al., 2021). Inhibition of SdrC self-assembly or binding to a competitive inhibitor β-neurexin was found to prevent SdrC-mediated adhesion and biofilm accumulation (Barbu et al., 2014; Feuillie et al., 2017). Collectively, the multiple functions of MSCRAMMs are essential for *S. aureus* colonization and survival within the host.

2.2. The NEAr Transporter (NEAT) motif family

The NEAr Transporter (NEAT) motif family largely comprises iron-regulated surface (Isd) proteins, which involves in bacterial survival in host with iron restriction (Fig. 1). Via binding of the NEAT motif to hemoglobin or heme, Isd proteins capture heme from hemoglobin, and then transport heme to reach the cytoplasm, allowing further iron acquisition. Number of NEAT motifs has been used to classify Isd proteins which have multiple functions in addition to iron acquisition. As previously found, IsdA played a critical role in the adherence of *S. aureus* to human desquamated epithelial cells during nasal colonization (Clarke et al., 2006), and decreased cellular hydrophobicity which further reduced the bactericidal activity of sebum fatty acids and increased *S. aureus* survival on human skin (Clarke et al., 2007). Similarly, IsdH was found to mediate inhibition of bacterial killing by neutrophils and further opsonophagocytosis (Visai et al., 2009). Upon host invasion, Isd proteins interact with other organisms including coronavirus. For examples, IsdA increased severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) replication, suggesting that pre-colonized bacterial infection exacerbated the symptoms of coronavirus disease 2019 (COVID-19) (Goncheva et al., 2023). IsdB had been found to function as the receptor for host protein vitronectin, facilitating adhesion and invasion of bacteria to epithelial and endothelial cells. In addition to *S. aureus*, vitronectin had been identified to serve as a receptor for various bacteria including *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, and *Escherichia coli* (Singh et al., 2010). As concluded, the structures and functions of NEAT domains have been well studied, with the molecular mechanism of how to recognize binding partners yet to be determined.

2.3. Three-helical bundles

The triple-helix bundle motif protein A (SpA) has five N-terminal tandem-linked triple-helix bundle structural domains (designated as EABCD), which bind to IgG and other ligands containing an Xr (with repeats) and an Xc (non-repeat) region (Fig. 1). SpA enhanced *S. aureus* virulence and its interaction with host cells to cause a variety of inflammatory diseases. As a survival strategy for *S. aureus*, SpA binds 'Fc' fragments of human immunoglobulin G (IgG-Fc) forming immune complex (Atkins et al., 2008). The von Willebrand factor binding to SpA between helices 1 and 2 as well as IgG Fc can cause inflammation and severe infections (O'Seaghdha et al., 2006). As a B-cell superantigen, SpA binds to the Fab region of immunoglobulin M through V_H region β-strands (Graille et al., 2000), and its interaction with tumour necrosis

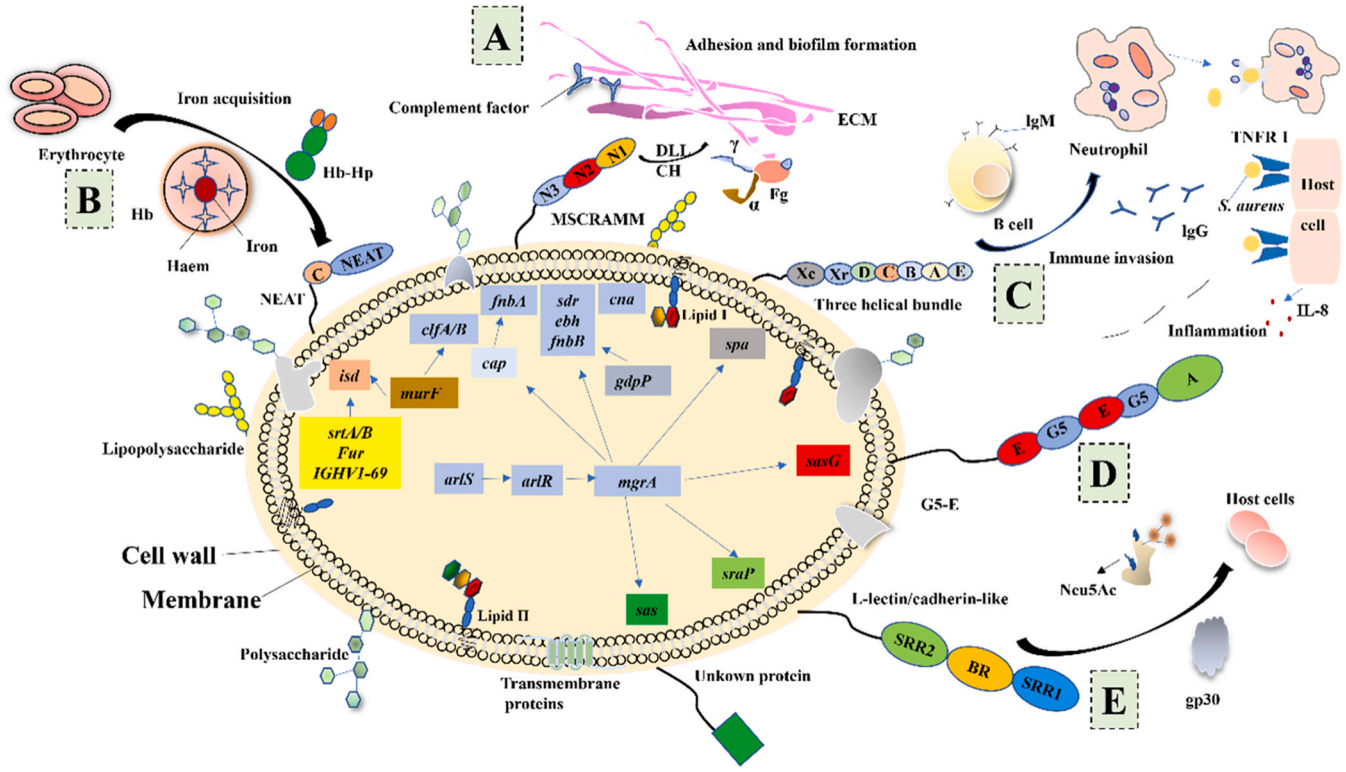

Fig. 1. Expression and function of CWAPs in *S. aureus*. Five groups of CWAPs classified based on the presence of motifs were shown. A. Proteins in MSCRAMM family possess an A structural domain which contains N1, N2, and N3 sub-structural domains. Through Dock, Lock, and Latch (DLL) or collagen hug (CH) mechanisms, MSCRAMM proteins bind to ligands on cell surface. The MSCRAMM family includes ClfA, ClfB, FnbpA, FnbpB, Sdr, and Cna, etc. B. The NEAr Transporter (NEAT) motif family largely comprises iron-regulated surface (Isd) proteins. Via binding of the NEAT motif to hemoglobin or heme, Isd proteins capture heme from hemoglobin, and then transport heme to reach the cytoplasm, allowing further iron acquisition. C. The triple-helix bundle motif protein A (SpA) has five N-terminal tandem-linked triple-helix bundle structural domains (designated as EABCD), which bind to IgG and other ligands containing an Xr (with repeats) and an Xc (non-repeat) region. D. In the G5-E repeat proteins family, structural domain of SasG is divided into subdomains A and B, with B consisting of a repeating region of alternating E and G5 subdomains. E. In legume lectin domain family, SraP consists of two serine repeat regions (SRRs), with one located in the short serine-rich repeat region (SSR1) at the N-terminal end followed by a ligand-binding BR structural domain, and the other as a long serine-rich repeat region (SSR2) presenting in SraP. Moreover, there are still some structurally uncharacterized CWAPs, such as SasX, SasB, SasL, bap, etc. Also, in the middle, a regulatory pathway controling expression of CWAPs genes including ArlRS two-component regulatory system and MgrA was illustrated.

factor receptor 1 (TNFR 1) and epidermal growth factor receptor (EGFR) is essential in pulmonary infections (Gómez et al., 2006, 2007). As reported, SpA altered the host immune response and thus contributed to sustained colonization of *S. aureus* in mice (Sun et al., 2018). To wrap up, the triple-helix bundles in *S. aureus* were pivotal in triggering inflammatory responses and evading host immune defenses during infection.

2.4. G5-E repeat proteins

In the G5-E repeat proteins family, SasG and Pls in *S. aureus* and Aap in *S. epidermidis* are closely associated, which have been well documented to be crucial in biofilm formation and pathogenicity (Conrady et al., 2008; Geoghegan et al., 2010). For SasG, its structural domain is divided into subdomains A and B, with B consisting of a repeating region of alternating E and G5 subdomains. SasG mediates intercellular adhesion through specific Zn^{2+}-dependent homophilic bonds between G5-E structural domains to facilitate host colonization (Conrady et al., 2013; Formosa-Dague et al., 2016; Mills et al., 2022), while adhesion of *S. epidermidis* to keratinocytes depends on the lectin subdomain within the A structural domain of Aap (Roy et al., 2021). In addition, the isolated uncanonical structural domains of both Aap and SasG are sufficient for binding to human host desquamated nasal epithelial cells (Clark et al., 2023). In SasG, domain A is dispensable for biofilm formation when domain B is present, while the number of B region influences the total length of this gene (Corrigan et al., 2007; Geoghegan et al., 2010). Both SasG and Eap play essential roles in the thickness of biofilm formation, while absence of sasG alone insignificantly influence the ruggedness and thickness of biofilm (Yonemoto et al., 2019). In addition, SasG is also involved in early macrophage interactions and increases inflammation in the early stages of bacterial pneumonia (Grousd et al., 2022). In summary, for the G5-E repeats family proteins such as SasG and Pls in *S. aureus*, their distinctive structural features facilitate intercellular adhesion and further host colonization, and thus such genes are important for biofilm formation and pathogenicity.

2.5. The legume lectin domain

Bacterial attachment is a key step to colonization and invasion, and the serine-rich adhesin of platelets (SraP) is an important class of adhesion factors in Gram-positive bacteria (Lizcano et al., 2012). SraP consists of two serine repeat regions (SRRs) (Fig. 1), with one located in the short serine-rich repeat region (SSR1) at the N-terminal end followed by a ligand-binding BR structural domain, and the other as a long serine-rich repeat region (SSR2) presenting in SraP. The large number of repeats in the SRR2 domain is responsible for the large size of most serine-rich repeat proteins (SRRPs). SraP-encoding bacteria possess a gene locus comprising glycosyltransferases (GtfA and GtfB) for glycosylation, along with co-secretory factors (SecY2 and SecA2) for SraP transport (Mistou et al., 2009; Zhou et al., 2011). As found, a legume-lectin region conferred SraP with binding of N-acetyl neuraminic acid (Neu5Ac) to salivary glycoprotein gp340, contributing to

S. aureus adhesion to host cells and virulence enhancement (Kukita et al., 2013; Yang et al., 2014). Collectively, the structure of the legume lectin domain contributes to adhesion and invasion of *S. aureus*.

3. Role of CWAPs in biofilm formation

The pivotal involvement of CWAPs in *S. aureus* during both biofilm formation and host invasion has been well studied. This section delves into the significant anchoring function exerted by CWAPs in biofilm development, including their multifaceted roles in facilitating *S. aureus* adhesion onto diverse surfaces, biofilm formation within authentic environmental contexts, and the potential mitigation of biofilm formation through targeted interventions was explored.

3.1. Cell wall anchoring of CWAPs

For CWAPs in *S. aureus*, sortases (SrtA and SrtB) recognize LPXTG or NPQTN motifs for anchoring these proteins to cell wall (Maresso et al., 2007). Mutations in sortases may lead to inability in covalent attachment between CWAPs and peptidoglycans, and further reduced adhesion to host cells and pathogenicity. Thus, SrtA and SrtB are considered to be promising targets to develop approaches for *S. aureus* treatment (Wu et al., 2019; Younis et al., 2019; Hussain et al., 2020; Wang et al., 2021c, 2021b, 2022b). As found, taxifolin, an inhibitor of SrtA, reduced biofilm initiation but failed to function on mature biofilm (Wang et al., 2021a). In addition to sortases, cell wall is another therapeutic alternative for *S. aureus* (García-Lara et al., 2005; Naclerio and Sintim, 2020; Molina et al., 2022). For example, the synthetic lipoglycopeptide dalbavancin had been recently observed to exert antibacterial effects by affecting the anchoring mechanism of Gram-positive bacteria (Molina et al., 2022).

However, it still remains controversial whether cell wall anchoring of CWAPs is essentially required for biofilm formation. As a dynamic process, location of CWAPs in cell wall closely relates to cell division, secretion, cell morphogenesis, and gene expression levels (Dramsi and Bierne, 2017; Sutton et al., 2021; Zhang et al., 2021). Recent studies had shown that SrtA mutants still produced small amount of biofilm, implying that other compounds or non-cell wall anchoring CWAPs may contribute to biofilm formation. In addition, biofilm forming capability varied among SrtA mutants, indicating that other genes may also play a role in biofilm formation (O'Neill et al., 2009; Yonemoto et al., 2019). As reported, autolysin Atl affected early-stage colonization by influencing the levels of fibronectin-binding proteins (FnBPs) and SpA on the cell wall surface (Leonard et al., 2023). Regardless of cell wall anchoring, SpA is positively correlated with biofilm formation, as either synthetic SpA or supernatant containing secreted SpA is sufficient to induce biofilm formation (Merino et al., 2009). Also, after cleavage of the anchoring structure by cytoplasmic hydrolase, SpA can be released and further secreted with its C-terminal attaching peptidoglycan (Becker et al., 2014; Rowan-Nash et al., 2019). Based on the importance of peptidoglycan, release of anchored CWAP may facilitate host invasion (Wang et al., 2022a). Thus, whether unanchored CWAPs could interact with other molecules (e.g. DNA) to compensate their involvement in biofilm formation, requires further studies (Kavanaugh et al., 2019; Yonemoto et al., 2019). However, such anchoring dependency may vary in different environments. As found, in an iron-deficient environment, cells relied on SrtB to anchor CWAPs for acquisition of elemental iron to further colonize within the host cell (Mazmanian et al., 2002; Gaudin et al., 2011; Bowden et al., 2018; Mathelié-Guinlet et al., 2020). It's noteworthy that conserved sequences are important for cell wall anchoring function. As reported, a point mutation in the fibronectin-binding protein center caused loss of CWA function of FnBPs, leading to dramatic reduction in adhesion to ligands and host cells (Grundmeier et al., 2004). Also, deletion of LPXTG motif in *sasG* led to secretion of its encoding protein to supernatant, instead of serving as a component of the cell wall (Yonemoto et al., 2019). Consequently, anchoring functioned by CWAPs under specific conditions is essentially required for adherence, biofilm establishment, and subsequent colonization in hosts for *S. aureus*.

3.2. Functioning on different surfaces

Biofilm formation of *S. aureus* on biotic and abiotic surfaces significantly differed at protein regulation level (Fig. 2). On biotic surfaces, CWAPs mediate bacterial adhesion and aggregation by binding to receptors or receptor ligands on the surface, which initiates biofilm formation and thus provides a protective barrier against mechanical shear, immune system attacks, and environmental stresses. Also, CWAPs facilitate bacterial invasion and infection by binding to host cell receptors, as well as colonization by binding to specific ligands on the host surface. Adhesion depends on both surface and CWAPs. For examples, higher FnBPs mediated adhesion was obtained from glass surface coated with fibronectin (Fn) (Xu et al., 2008), and thrombin in the plasma-coated environment inhibited *S. aureus* growth due to the within host. While conversion of the binding ligands of CWAPs (such as FnBPs) into fibrinogen by the thrombin-thromboplastin complex was important for biofilm formation on plastic tissue culture coverslips with 0.3% fibrinogen/human serum (Akiyama et al., 1997). The use of thrombin inhibited the growth of *S. aureus* in the plasma-coated environment within host. As a consequence, understanding the role of CWAPs in biofilm formation aids in surface modification and coating design of medical devices to inhibit biofilm formation and reduce infection risk.

On abiotic surfaces, CWAPs typically undergo nonspecific binding, primarily relying on electrostatic interactions, van der Waals forces, and hydrophobicity (Fig. 2). This may cause conformational changes or proteins aggregation on abiotic surfaces, and further affect bacterial adhesion and biofilm formation. Thus, difference in binding mechanisms between CWAPs and surfaces leads to variations in bacterial adhesion, biofilm formation and pathogenicity. In addition, different surface materials exhibited variations in their binding capabilities, which also serve as influential factors in biofilm formation. During biofilm quantification, difference in hydrophilicity or hydrophobicity caused by culture plates materials also affected biofilm formation, particularly for CWAPs that relied on non-covalent binding forces. Up to date, studies on *S. aureus* biofilm formation are often conducted on polystyrene surfaces. For example, significant upregulation of genes encoding FnbpA, FnbpB, ClfB, and ClfA was found from biofilms (24 h) (Atshan et al., 2013; Vlaeminck et al., 2022), and ClfA-mediated biofilms could be influenced by shear forces exerted by fluid flow. Aside from the surface properties and micro-environments, variations in CWAPs expression and their composition may also contribute to the difference between *in vitro* and *in vivo* biofilms. Collectively, CWAPs adhere to various surfaces mainly through a combination of protein-protein interactions (biotic surface) or physical processes (abiotic surface), and variations in biofilms formed on plates with different physical properties were evident. Thus, surface modifications may serve as an effective method to inhibit microbial colonization.

4. Functioning of CWAPs during biofilm formation

A number of proteins function in colonization of *S. aureus* on biotic or abiotic surfaces, with CWAPs as an important group. *S. aureus* strains with strong biofilm-forming ability commonly carry CWAPs genes, such as *clfA*, *clfB*, *fnbpA*, and *fnbpB*, etc (Nemati et al., 2009). Here, the expression of CWAPs genes as well as their function is summarized according to different stages of biofilm formation (Table 1, Fig. 1).

In the early stage of biofilm formation, ClfA, ClfB, FnbpA, and FnbpB within MSCRAMM family interact with proteins (homogeneous interactions) or ligands (heterogeneous interactions) to mediate microbial adhesion and thus initiate biofilm formation. In addition, a few other factors including fluid flow (shearing force), chemical substances or polymers, as well as CWA effect, also influence CWAPs interaction

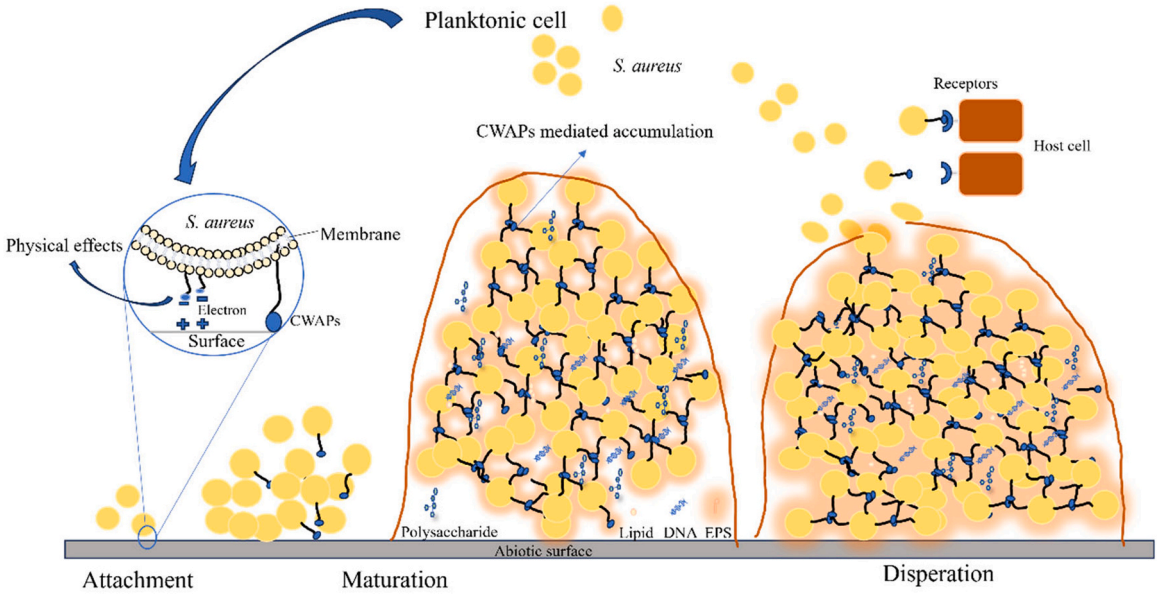

Fig. 2. The role of CWAPs in *S. aureus* biofilm formation. In the initial stages of biofilm formation, CWAPs of *S. aureus* engage in nonspecific binding through van der Waals forces and hydrophobic interactions. While on biotic surface (such as host cell), CWAPs bind to receptors or receptor ligands, facilitate adhesion and further biofilm formation. As the biofilm matures and disperses, *S. aureus* spreads to other uninfected surfaces for adhesion to further successful colonization.

(Burian et al., 2021). ClfA is an essential contributor for biofilms at early stage. For examples, *clfA* was the only significantly upregulated gene in biofilms formed by MRSA strains USA300 and HEMRSA-15 (24 h, on polystyrene surfaces) (Vlaeminck et al., 2022), and ClfA was the major contributor to aggregation of *S. aureus* in postoperative joint fluid (simulating *in vivo* conditions) despite influence from shear forces generated by dynamic synovial fluid (Staats et al.). ClfB functions in early biofilm formation independently of binding activity to ligand fibronectin, which becomes essential for biofilm formation in the absence of Ca^{2+} (Abraham and Jefferson, 2012; Abraham et al., 2012). Also, ClfB mediates adhesion to keratinocytes of atopic dermatitis patients through the formation of mechanically stable DLL bonds with ligands on the skin surface, and strong binding occurs between ClfB and skin ligands exposed on keratinocytes with low natural moisturizing factor (NMF) (Feuillie et al., 2018). SdrC, SdrD, and SasG are also contributor for adhesion to host cells (Roche et al., 2003; Corrigan et al., 2009; Barbu et al., 2010; Askarian et al., 2016, 2017).

In proliferation and maturation stages of biofilm, FnBPs play important roles in glucose and pH-induced conditions (O'Neill et al., 2009), and Zn^{2+} is essential for functioning of FnBPs (Geoghegan et al., 2013). Aside from FnBPs, Zn^{2+} may also be important for other substances, such as the Atl amidase domain activity (Zoll et al., 2010). It is noteworthy that N3 structure of A domain of FnBPs plays an essential role in accumulation and proliferation, independently of the binding activity between FnBPs and ligands (Kwon et al., 2013; Herman-Bausier et al., 2015). For invasion, FnBPs are crucial for highly invasive *S. aureus* (Pereyra et al., 2016) despite their unequal contribution (such as FnbpA and FnbpB). For example, MRSA strains in ST59-SCCmec IV-t437 clone carried FnbpA (100% carriage rate) but FnbpB (Yang et al., 2017). Remarkably, carriage of CWAPs genes correlates with biofilm formation capability. As reported, presence of *sasG* gene was highly associated with strong biofilm formers ($p = 0.151$) (Jones et al., 2023). SasG requires a minimum of 5 B repeat structures for steric hindrance effects, and its expression masks binding of other CWAPs to fixed ligands such as IgG, fibrinogen, and fibronectin (Corrigan et al., 2007). Eap and SasG play roles in biofilm formation, and loss of both genes may lead to incapability of forming thick and abundant biofilms (Yonemoto et al., 2019). For SdrC, its N2 domain mediates homologous interactions, facilitating cell adhesion on abiotic surfaces, despite its role in biofilm formation being dispensable. As reported, the expression level of SdrC significantly elevated during biofilm formation (particularly at 24 and 48 h), along with high expression of other binding proteins (Resch et al., 2005; Barbu et al., 2014; Feuillie et al., 2017). Quorum sensing Agr system is also closely associated with expression of CWAPs. As reported, from *S. aureus* biofilm formed under burn rat serum conditions (simulating burn patients), increased binding of CWAPs to related ligands (such as fibrinogen or human fibronectin) as well as decrease in Agr, were found (Yin et al., 2017; Peng et al., 2019). Furthermore, on biotic surfaces, the impact of human blood on the *sdrE*, *sdrC*, and *sdrD* genes differed. In detail, SdrD functions in interaction between pathogen and human immune system or serum, or it may elicit specific reactions to the nutrients/other factors present in human blood, which further contributes to host colonization (Sitkiewicz et al., 2011). A competitive inhibitor, the host protein β-neurexin peptide, binds with high affinity to the N2N3 domain of SdrC which impairs biofilm formation. Similar inhibition on SdrC was also found in Mn^{2+} (Barbu et al., 2014; Feuillie et al., 2017). SasX, serving as effector other than regulator, also participates in biofilm formation, as supplementation of SasX restores biofilm formation (Li et al., 2012; De Backer et al., 2019).

In addition, during biofilm formation, dependence on CWAPs varies among different conditions and stages, and complementary interplay among CWAPs compensates function loss of one single CWAPs. Expression level of FnbpA, FnbpB, and ClfB genes significantly increased (approximately threefold) in early biofilms (24 h, on polystyrene surfaces), and then decrease in mature biofilms (48 h) (Atshan et al., 2013). Also, functioning of FnBPs requires the production of Atl and eDNA on hydrophilic and hydrophobic polystyrene (Houston et al., 2011).

In summary, the interplay between various CWAPs and ligands plays a critical role in adhesion, biofilm proliferation and maturation, as well as colonization in host.

5. Targeting CWAPs approaches

Targeting CWAPs and their highly homologous surface protein clones has emerged as approaches to inhibit *S. aureus* biofilm formation (Belyi et al., 2018; Martín et al., 2018; Carothers et al., 2020; Dey et al., 2021). Recently, the cloned cell surface-exposed rSesC protein, which shares high homology with ClfA, had been utilized for biofilm inhibition

in *S. aureus*, and antibodies from PIA and rSesC mixture showed significantly higher efficacy compared to PIA and rSesC alone (Mirzaei et al., 2021). Another approach targeting ClfA had employed microbubbles (MB) with subsequent disruption by ultrasound, which also resulted in reduced biofilm and cell death (Caudwell et al., 2022). Also, a natural compound Aloe-emodin was found to inhibit the initial attachment of biofilm formation in *S. aureus* by reducing extracellular proteins production (Xiang et al., 2017). It is noteworthy that CWAPs-mediated DNA to the biofilm matrix also contributes to biofilm formation, including structural stability, antimicrobial resistance, gene transfer, environmental adaptation, survival and persistence of cells (Yonemoto et al., 2019). For example, DNA binding in biofilm matrix was found to enhance horizontal gene transfer and further facilitate exchange of beneficial genes within the microbial community (Marraffini and Sontheimer, 2008; Lindsay, 2014; Partridge et al., 2018).

Despite a large number of anti-biofilm strategies aiming at CWAPs disruption or ligands masking, a few significant limitations still remain. Firstly, these studies largely utilized the surface proteins from abiotic surfaces which is different from the actual *in vivo* conditions. Secondly, early biofilms (up to 24 h) have been widely used, with mature biofilms rarely touched upon.

6. Association of CWAPs genes with clonal lineages

Since *S. aureus* from different clonal lineages exhibit diversity in pathogenicity, antimicrobial resistance and biofilm forming capability, this section aims to decipher the intricate correlation between CWAPs genes and the clonal lineages.

6.1. CWAPs genes involved in biofilm formation

Infections caused by biofilm-forming *S. aureus* strains often result in a significant increase in morbidity and mortality rates (Moormeier and Bayles, 2017), and thus presence of CWAPs genes may provide the host with a wide range of characteristics, including microbial colonization, biofilm formation and invasion.

In *S. aureus*, *clfA* and *clfB* genes were commonly identified with high rate. As found, most *S. aureus* strains isolated from children carried CWAPs genes including *fnbA*, *fnbB*, *clfA*, *clfB*, and *cna*, belonging to ST22-t309, ST59-t437, and ST338-t437 (Ma et al., 2022). For *S. aureus* isolated from milk, the prevalent ST188 clone was found to be associated with strong biofilm formation and high carriage of CWAPs genes (such as *cna*, *clfA*, *clfB*, *fnbA*, and *fnbB*) (Dai et al., 2019), and from mastitic milk, high incidence of *fnbA*, *cna*, and *clfA* (89.5%) was abtained (Ibrahim et al., 2022). In Jingzhou of China, 100% identification rates for *clfB*, *clfA* and *fnbA* were obtained from the prevalent clones SCC*mec* III-t030 (n=24) and SCC*mec* IV-t437 (n=14) (Peng et al., 2018; Wang and Zhang, 2022). High colonization of *S. aureus* was found in the nasal cavity of Thai children, with common carriage of *fnbA* (93.59%) and *cna* (61.54%) and strong biofilm formation (95% of isolates) (Tangchaisuriya et al., 2014). Presence of *cna* was distinctive feature of CC30, a clone with a higher mortality in bloodstream infections (Aamot et al., 2012; Blomfeldt et al., 2016b, 2016a). Aside from this clone, in Nigeria and South Africa, *cna* carriage was positively associated with t037-CC8-MRSA-SCC*mec* III clone, which was distinguished from t064-CC8, t1257-CC8, t045-CC5, t951-CC8, t2723-CC88, t6238-CC8, and untypeable-CC8 (Shittu et al., 2021). However, due to the complementary interplay among CWAPs, MSCRAMMs genes (*clfA/B*, *ebpS*, *eno*, *fnbA*, *map*, *sdrC*, and *vwb*) could also be detected from human isolates regardless of their ability to form biofilms (Achek et al., 2020). In osteomyelitis in Italy, *S. aureus* isolates from prevalent clones CC22, CC5, CC8, CC30, and CC15, carried a variable combination of CWAPs genes that caused high pathogenicity (Pimentel de Araujo et al., 2022).

In addition, expression and production of CWAPs genes, as well as subsequent functioning, may also correlate with clonal background of *S. aureus*. The A structural domain of FnbpB in *S. aureus* carrying clonal complex 1 promoted biofilm formation, but FnbpB might not promote tegument formation in a ligand-bound manner (Keane et al., 2007; Henderson and Geoghegan, 2023). Higher biofilm formation was found from SasG allele mutants in CC5 and CC8 clones (Carrera-Salinas et al., 2022).

6.2. CWAPs genes involved in adhesion and colonization

Adhesion to host cells is a crucial step in the colonization of *S. aureus*, and several CWAPs genes are involved in this process.

CWAPs genes involved in adhesion had been found in more than 96% of *S. aureus* isolates, frequently associated with ST5 and ST8, and CC30 and CC1 (Afzal et al., 2022). Adhesion mediated by CWAPs was intricately linked to cutaneous disorders, as FnBPs and ClfB initiated adhesion to host cells and SpA mediated pro-inflammatory binding to TNFR-1 on keratin-forming cells. Thus, CC1 strains is the prevalent spectrum on the skin of children with atopic dermatitis (Mulcahy et al., 2012; Chen et al., 2016; Geoghegan et al., 2018; Sultana and Bishayi, 2018). From another report on atopic dermatitis, ClfB ligand binding activity was detected in all isolates from major clonal complexes CC1 (20.45%), CC45 (15.9%), CC8 (13.63%) and CC5 (13.63%) (Fleury et al., 2017), whereas amino acid sequence variations in ClfB of different origin further influenced the attachment efficacy to keratinocytes. *Sdr* carriage was found to correlate with *S. aureus* lineages. As reported, majority of clinical *S. aureus* isolates (95.5%) carried at least *SdrC, SdrE* or *SdrD* genes, and the association between *SdrE* carriage and treatment burdening was revealed (Liu et al., 2015; Lee et al., 2018). In bovine mastitis, high carriage of ClfB and SdrCDE (82.4%) was also found (Klein et al., 2012). For *S. aureus* from healthy nasal cavities, mutations in SdrD alleles were highly associated with CC84, and such mutations caused structural variants in the N3 subdomain involved in ligand binding via DLL mechanism which further led to insufficient bacterial adhesion to human keratinocytes (Wang et al., 2013; Ajayi et al., 2018). Other *sdrD* mutants were more phylogenetically related, such as ST22 and ST109 (Ajayi et al., 2018), suggesting likeliness of horizontal gene transfer during evolution of *S. aureus* (Lindsay, 2014; Cafini et al., 2017). A 126 amino acid sequence containing the CnaB domain was highly conserved within SdrC, SdrD, and SdrE proteins, which served as a potential vaccine candidate (Becherelli et al., 2013). FnBPA and FnBPB encoded by *fnb* genes are in different evolutionary trajectories, and the process evolved through multiple mutations and recombinations with functional retention (Murai et al., 2016; Speziale and Pietrocola, 2020). High carriage of *fnb* was reported from *S. aureus* isolates from Japan, and this ST59 were more associated with toxin genes than other ST clones, which showed increasing occurrence in Asian countries (Wang et al., 2016). As a colonization contributor, SpA in ST88 strains affected the host IgG response and further aided in the sustained colonization of *S. aureus* colonization in mice (Sun et al., 2018). In addition, other virulence genes, such as *bbp, pvl, sei, sen* and *seo* were associated with specific sequence types (ST)30 and CC30 (Cavalcante et al., 2021).

Collectively, presence and expression of CWAPs genes are essential for *S. aureus* colonization, biofilm formation and pathogenesis, which is closely associated with clonal lineages along with other bacterial characteristics such as virulence and antimicrobial resistance. Also, based on the thorough analysis of CWAPs genes homology and acquisition of highly conserved regions, future studies could delve into development of vaccine and other therapeutic approaches.

7. Conclusion and outlook

In this review, we firstly focus on the structural features of CWAPs, including their intracellular function and interactions with host cells, as well as the functions and ligand binding of CWAPs in different stages of S. aureus biofilm formation. Up to date, over 20 distinct CWAPs have been identified in *S. aureus*, and their roles are categorized into five groups based on the presence of motifs, including MSCRAMM family,

Table. 1
The role of CWA in biofilm formation.

Biofilm formation related CWAPs	Ligand	Experimental surface	Influence factors	References
ClfA	DLL (fibrinogen)	Abiotic surfaces	Affected by shear force	(Staats et al.; Vlaeminck et al., 2022)
ClfB	DLL (ligand) or non-ligand	Biosurfaces and abiotic surfaces	ClfB-dependent in the absence of Ca^{2+}	(Abraham and Jefferson, 2012; Abraham et al., 2012; Atshan et al., 2013; Feuillie et al., 2018)
FnbpA	A Structural domain homogeneous interactions	Abiotic surfaces	Zn^{2+}-mediated; anchoring -dependent, stable expression under anaerobic conditions for 48 h	(Geoghegan et al., 2013; Kwon et al., 2013; Herman-Bausier et al., 2015; Yeswanth et al., 2017)
FnbpB	A Structural domain homogeneous interactions	Abiotic surfaces	Anchoring -dependent; pH effects	(O'Neill et al., 2009)
SdrC	N2 structural domain homo- and hydrophobic interactions	Abiotic surfaces	Peptide damage by the host protein β-neuropeptide; inhibited by Mn^{2+}	(Resch et al., 2005; Barbu et al., 2014; Feuillie et al., 2017)
SasG	G5 structural domain homogeneous interaction	Abiotic surfaces and biosurfaces	Anchoring -dependent; Binding eDNA; Zn^{2+}-dependent; dependent on the number of B repeats	(Corrigan et al., 2007; Conrady et al., 2008, 2013; Formosa-Dague et al., 2016; Yonemoto et al., 2019)
SpA	A compound on the cell surface	Abiotic surfaces	Anchoring -independent	(Merino et al., 2009)
Bbp	Fgα	/	Hydrogen bonding	(Patti et al., 1994; Gomes et al., 2023)
Bap	Hydrophobic forces in homogeneous interactions	Abiotic surfaces	Normal pH conditions also promote the formation of biofilm; involvement of PIA	(Shukla and Rao, 2022)
SraP	Gp340	Abiotic surfaces (Gp340 coating surface)	Other proteins involved	(Osei et al., 2022)

NEAT motif family, three-helical bundles, G5-E repeat proteins, and legume lectin domain. Then, the roles of CWAPs in different biofilm processes with regards to development of therapeutic approaches are clarified, followed by the association between CWAPs genes and clonal lineages. The interplay between various CWAPs and ligands plays a critical role in adhesion, biofilm proliferation and maturation, as well as colonization in host. Targeting CWAPs and their highly homologous surface protein clones has emerged as approaches to inhibit *S. aureus* biofilm formation. Despite many anti-biofilm strategies aiming at CWAPs disruption or ligands masking, a few significant limitations remain. Firstly, these studies largely utilized the surface proteins from abiotic surfaces which are different from the actual *in vivo* conditions. Secondly, early biofilms (up to 24 h) have been widely used, with mature biofilms rarely touched upon. Presence and expression of CWAPs genes are essential for *S. aureus* colonization, biofilm formation and pathogenesis, which is closely associated with clonal lineages along with other bacterial characteristics such as virulence and antimicrobial resistance. Also, based on the thorough analysis of CWAPs genes homology and acquisition of highly conserved regions, future studies could delve into development of vaccine and other therapeutic approaches. Comprehensive knowledge and clearer understanding on the CWAPs of S. aureus and their roles in biofilm formation in this review may further aid in prevention and treatment infection and vaccine development.

Future research could focus on surface modifications or coatings which inhibited *S. aureus* biofilm formation on biotic and abiotic surfaces. Materials with altered surface properties, such as enhanced hydrophilicity or modified charge characteristics, are to be studied to reduce bacterial attachment and biofilm formation. Understanding the functional role of CWAPs on different stages of biofilm formation could contribute to the development of effective antimicrobial agents inhibiting CWAP binding or interfering with biofilm formation. Further experiments are crucial to confirm if certain substances influence CWAPs anchoring to the cell wall and to assess their potential impact on biofilm formation. This would provide new targets for developing novel antibacterial drugs and provide more effective treatment options for bacterial infections and diseases related to biofilms.

CRediT authorship contribution statement

Xuejie Li: Writing – review & editing, Conceptualization. **Gamini Seneviratne:** Supervision. **Junyan Liu:** Writing – original draft, Funding acquisition, Conceptualization. **Zhenbo Xu:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Yaqin Li:** Writing – original draft, Conceptualization. **Thanapop Soteyome:** Writing – review & editing, Supervision. **Aijuan Xu:** Writing – review & editing, Validation. **Qin Ma:** Writing – review & editing, Validation. **Lei Yuan:** Writing – review & editing, Validation.

Declaration of Competing Interest

There are no conflicts to declare.

Data availability

Data will be made available on request.

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