Published in final edited form as:
Semin Immunopathol. 2012 March ; 34(2): 201–214. doi:10.1007/s00281-011-0296-2.

Molecular basis of *Staphylococcus epidermidis* infections[1]

Michael Otto
Pathogen Molecular Genetics Section, Laboratory of Human Bacterial Pathogenesis, NIAID, NIH; 9000 Rockville Pike, Bethesda, MD 20892, USA

Abstract

Staphylococcus epidermidis is the most important member of the coagulase-negative staphylococci and one of the most abundant colonizers of human skin. While for a long time regarded as innocuous, it has been identified as the most frequent cause of device-related infections occurring in the hospital setting and is therefore now recognized as an important opportunistic pathogen. *S. epidermidis* produces a series of molecules that provide protection from host defenses. Specifically, many proteins and exopolymers, such as the exopolysaccharide PIA, contribute to biofilm formation and inhibit phagocytosis and the activity of human antimicrobial peptides. Furthermore, recent research has identified a family of pro-inflammatory peptides in *S. epidermidis*, the phenol-soluble modulins (PSMs), which have multiple functions in immune evasion and biofilm development, and may be cytolytic. However, in accordance with the relatively benign relationship that *S. epidermidis* has with its host, production of aggressive members of the PSM family is kept at a low level. Interestingly, in contrast to *Staphylococcus aureus* with its large arsenal of toxins developed for causing infection in the human host, most if not all "virulence factors" of *S. epidermidis* appear to have original functions in the commensal lifestyle of this bacterium.

Keywords

Staphylococcus epidermidis; biofilm; phenol-soluble modulins; polysaccharide intercellular adhesin; device-related infections; hospital-associated infections

1. Introduction

Coagulase-negative staphylococci (CNS) are a prominent part of the normal flora of human skin. Certain CNS species prefer specific niches, while others occur almost everywhere on our body [1,2]. In contrast to *Staphylococcus aureus*, CNS colonize every human being. This includes *Staphylococcus epidermidis*, which is the most frequently encountered CNS species on the human body and a common colonizer of the axillae, head, and nares [1,3]. Colonization with *S. epidermidis* may play an important role for the maintenance of a healthy skin flora, by competition with potentially harmful microorganisms such as in particular *S. aureus*. On the other hand, *S. epidermidis* is now also being recognized as an important opportunistic pathogen that can cause significant problems when breaching the epithelial barrier, especially during biofilm-associated infection of indwelling medical devices. Here, I will present molecular factors that are involved in the success of *S. epidermidis* as a colonizer and pathogen, with a specific focus on the interaction with *S.*

[1]This article is published as part of the Special Issue on Immunopathology of staphylococcal infections [34:3]

Phone: 301 443 5209 Fax: 301 480 3633 motto@niaid.nih.gov.

aureus and the different “approaches” of these two related bacteria to evade human immune defenses during colonization and infection.

2. Diseases caused by *S. epidermidis* and other coagulase-negative staphylococci

Most diseases caused by *S. epidermidis* and other CNS are of a chronic character and occur as device-related infections (such as intravascular catheter or prosthetic joint infections) and their complications [4]. *S. lugdunensis* represents a certain exception among the CNS, as it is more often involved in severe infections that resemble those caused by *S. aureus* [5–7]. In CNS device-related infections, complete removal of the infected device and prolonged antibiotic therapy are often necessary. CNS bloodstream infections originating from intravascular catheter infections are estimated to reach 250,000 cases per year in the U.S., with a mortality rate of 1–25%. These infections represent a significant burden for the public health system, with a cost of $25,000 per episode and an excess hospital stay of > 7 days [8,9]. More severe manifestations, such as prosthetic valve endocarditis (PVE), are rare compared to device-related infections. However, CNS are among the most frequent causes of PVE (15–40%) [10]. Of note, neonates represent a particularly high-risk group for CNS infections [11], with 31% of all neonatal infections and 73% of neonatal bacteremias attributable to CNS [12].

3. Antibiotic resistance

Resistance to methicillin is widespread among hospital isolates of CNS and in particular, *S. epidermidis* (methicillin-resistant *S. epidermidis*, MRSE), ranging globally from 75–90% [13]. It is due to the presence of the *mecA* gene, which codes for a penicillin binding protein, PBP2a, with decreased affinity to methicillin [14]. Heteroresistance, which means that only one in 10^4 to 10^8 cells shows a high level of methicillin resistance, occurs in CNS similar to *S. aureus* [15]. Resistance to aminoglycosides and macrolides, and to a lesser extent, tetracycline, chloramphenicol, and clindamycin is also frequently observed among hospital-associated *S. epidermidis* strains [4]. Intermediate resistance to vancomycin (VISE, vancomycin intermediate resistant *S. epidermidis*) is on the rise [16]; however, spread of vancomycin high-level resistant strains has not been reported. Among the newer antibiotics, resistance is still very rare to linezolid and streptogramins, and not reported for daptomycin or tigecycline [4]. Of note, non-specific resistance (tolerance) by biofilm formation is of great concern in CNS infections and will be discussed below.

4. Virulence factors of *S. epidermidis*

S. epidermidis is by far the best studied member of the CNS in terms of the knowledge that we have on molecular mechanisms of virulence (Tab. 1). For the purpose of the present review, the definition of `virulence factors” will be broad, comprising genes and proteins that facilitate the establishment of infection and persistence of the organism in the human body. It will become clear that most of these factors also have important roles in the commensal life of *S. epidermidis* as an innocuous inhabitant of the human skin and may thus not be regarded as “virulence factors” sensu stricto.

4.1 Biofilms

S. epidermidis, like many other CNS, is an excellent biofilm former, and most *S. epidermidis* infections involve biofilms. Biofilms are sticky, surface-attached agglomerations of bacteria that are embedded in an extracellular matrix and provide protection from antibiotics and mechanisms of host defense [17,18]. For many antibiotics, MIC values against bacteria in

biofilms can be higher by several logs compared to those against planktonic (free-floating) bacteria.

The mechanisms underlying the protective features of biofilms are multiple and may be different for a specific antibiotic or host defense mechanism. First, the matrix represents a mechanical barrier that is hardly penetrable for immune cells. However, there are also reports suggesting that, for example, neutrophils penetrate deeply into bacterial biofilms [19], likely through the matrix-free channels that are characteristic components of the three-dimensional biofilm structure. Nevertheless, phagocyte activity is commonly regarded as severely hampered by biofilm formation. For *S. aureus*, this has recently been shown clearly by Thurlow et al. [20]. Furthermore, limited diffusion through the extracellular matrix contributes to biofilm tolerance towards some antibiotics [21]. This is the case for example for ciprofloxaxcin and biofilms of *Pseudomonas aeruginosa* [22]. In contrast, other antibiotics have been shown to diffuse easily into the biofilm matrix, such as rifampin, vancomycin, and daptomycin in *S. epidermidis* biofilms [23,24]. Second, biofilms are to some extent physiologically “dormant” - showing reduced activity of many active cell processes such as cell division, protein synthesis, or DNA replication [21]. This specific physiological state of biofilms significantly decreases the efficacies of many antibiotics that target those processes, including for example the large number of protein synthesis inhibitors and the cell wall-active beta-lactam antibiotics. Third, biofilms may comprise an increased number of so-called “persister” cells, which show increased tolerance to antibiotics [25]. Recently, it was shown that *S. epidermidis* biofilms contain a high number of persister cells upon antibiotic exposure [26]. Finally, biofilms may show over-production of proteins or other biopolymers that contribute to resistance or tolerance [27].

4.1.1 *S. epidermidis* biofilms protect from mechanisms of innate host defense —Many of the protective mechanisms of biofilms toward host defenses, in particular those of innate host defense, have been analyzed in *S. epidermidis*. Mechanisms of innate host defense allow the human body to respond swiftly to an infection. They are triggered by the recognition of invariant structures on the bacterial surface, such as peptidoglycan, lipopeptides, lipoteichoic acids, or even some species-specific molecules such as the staphylococcal phenol-soluble modulins (PSMs) discussed below. Innate host defense comprises mainly the activity of phagocytes, antimicrobial peptides (AMPs), and the complement system.

It has been suggested early that the main biological purpose of the *S. epidermidis* “slime” substance, now called extracellular biofilm matrix, is to prevent ingestion of bacteria by phagocytes. Beginning in the 1980s, several reports were published providing evidence for that function [28–30]. Recent research has given more mechanistic insight, showing that *S. epidermidis* biofilms protect from neutrophil-dependent killing by complement inactivation via prevention of the deposition of C3b and immunoglobulin G (IgG) [31]. Furthermore, the extracellular matrix decreases the activity of antimicrobial peptides (AMPs), likely mostly by hindering them from reaching their predominant target, the cytoplasmic membrane [32].

4.1.2 Molecular mechanisms contributing to biofilm development—Biofilm development proceeds in 3 steps: initial adhesion, intercellular aggregation and accumulation, and final detachment [33]. Initial adhesion may occur to abiotic surfaces, such as the uncovered plastic surface of indwelling medical devices, or to biotic surfaces, such as tissues or human matrix protein-covered devices. Intercellular aggregation is accomplished by a series of matrix proteins and non-proteinaceous polymeric substances. In addition, more recent research has indicated a key role of surfactants in biofilm detachment [34–36]. Specific molecules involved in *S. epidermidis* adhesion, aggregation, biofilm structuring, and detachment will be presented in the following. First, proteins and polymers involved in

adhesion and/or accumulation will be discussed. Many of these have been implicated with both adhesion and accumulation. Finally, recent work on biofilm structuring and detachment will be presented.

MSCRAMMs: Several MSCRAMMs (microbial surface components recognizing adhesive matrix molecules) [37] play a role in tethering *S. epidermidis* cells to tissue or matrix protein-covered device surfaces. This may or may not ultimately lead to biofilm formation, but in any case is a crucial step for *S. epidermidis* persistence in or on the human body during colonization and infection. Similar to *S. aureus*, *S. epidermidis* has several MSCRAMMS for that purpose, with specificities for a series of different human matrix proteins [38]. This functional redundancy underscores the importance that the establishment of tissue adhesion has for *S. epidermidis* physiology. For example, MSCRAMMs of *S. epidermidis* accomplish binding to fibrinogen (SdrG/Fbe) [39,40], fibronectin (Embp) [41], vitronectin (AtlE, Aae) [42,43], and collagen (GehD) [44]. The fibrinogen and fibronectin binding proteins represent MSCRAMMs sensu stricto, with sortase-catalyzed covalent anchoring to peptidoglycan [45] and primary function as adhesins, while AtlE and Aae are non-covalently surface bound autolysins with adhesive in addition to their primary cell wall turnover functions [46]. Finally, GehD is a lipase that also appears to have an unrelated function as binding protein [44].

PIA: The exopolysaccharide polysaccharide intercellular adhesin (PIA), also named poly-N-acetylglucosamine (PNAG) was identified as the main constituent of the *S. epidermidis* extracellular matrix substance (“slime”) in 1996 by the group of Dietrich Mack in Hamburg, Germany [47]. While minor uncertainties persist about partial N-succinylation and yet not further identified variants of PIA, the main PIA exopolysaccharide is a linear N-acetylglucosamine polymer with partially N-deacetylated amine groups. It has a chain length of more than 130 residues in average. Notably, the sugar moieties are linked in β1–6 linkage, which contrasts one of the most abundant poly-glucosamines in nature, chitin, which has β1–4 linkages [47] (Fig. 1).

PIA is synthesized by the gene products of the *ica* operon, *icaA*, *icaD*, *icaB*, and *icaC* [48]. Adjacent to the *ica* operon is a regulatory gene, *icaR*, that is involved in the multifaceted regulation of *ica* gene expression [49–54]. IcaA is a glucosaminyl transferase that was shown to transfer glucosamine residues from UDP-glucosamine to a growing chain of pre-PIA [55]. It requires IcaD for full activity, but the detailed role of IcaD is not known. Both proteins are located in the cytoplasmic membrane. Presumably, IcaC, another membrane protein, exports the growing chain of pre-PIA out of the cell. This was speculated based on membrane location and the fact that in an *icaC* mutant, chain elongation stops at about 15 residues, also suggesting that chain elongation and export are coupled and the IcaA, IcaD, and IcaC proteins may form a complex [55]. Pre-PIA is N-deacetylated after export by the IcaB enzyme, which is a surface-attached PIA N-deacetylase [56]. Deacetylation is crucial for the multiple roles of PIA discussed below [56]. It also significantly increases immunogenicity of the PIA polymer [57].

As expected, a correlation between PIA production and biofilm formation among a collection of clinical *S. epidermidis* strains was found early after discovery of the polymer [58], and PIA has long been regarded as indispensable for *S. epidermidis* biofilm formation. However, strains were found more recently, in which in-vitro and in-vivo biofilm formation is independent of PIA and in which proteins functionally substitute for PIA [59,60]. Interestingly, there is evidence indicating that PIA-dependent biofilms form more robust biofilms than those exclusively formed by proteinaceous factors [60]. Furthermore, PIA was found to have multiple, additional roles in immune evasion that exceed a mere contribution to intercellular aggregation in biofilms [56]. For example, PIA was described as the major *S.*

epidermidis hemagglutinin [61]. Moreover, PIA reduces the activity of AMPs and killing by human neutrophils [56]. As the latter effects were observed after disruption of cell clusters by sonication, they are likely at least in part independent of intercellular aggregation, due only to the layer of PIA that surrounds a single *S. epidermidis* cell. PIA protects from the activity of both positively and negatively charged AMPs, indicating that different mechanisms may contribute to PIA-mediated resistance to AMPs, such as sequestration in addition to repulsion [56,32]. PIA was also reported to induce IL-8 expression in human astrocytes in a TLR2-dependent fashion [62]. However, this was not substantiated using isogenic *ica* deletion mutants, which is crucial when analyzing pro-inflammatory activities of bacterial compounds, because they almost never can be purified without leaving traces of known pro-inflammatory agents such as lipopeptides. This is especially true in case of the complicated purification of PIA [47,63].

The contribution of PIA to virulence has been monitored in a multitude of animal studies of device-related infection. These studies used mice, rats, rabbits, or *Caenorhabditis elegans* and mutants in the *ica* operon of *S. aureus* or *S. epidermidis*. A majority of studies found that PIA contributed to virulence in those models [64–67]. This includes a study in which specifically the role of IcaB-dependent deacetylation was investigated and found to have a significant impact on virulence [56]. However, some studies failed to detect a role of PIA in the pathogenesis of biofilm-associated infection [68,69]. While those latter studies are often exclusively cited when aiming to emphasize the importance of protein-dependent biofilm formation, it must be stressed that (i) differences in the experimental setup may have led to the negative outcome and (ii) those studies contradict a larger series of studies showing a significant role of PIA in biofilm-associated infection.

Teichoic acids: Teichoic acids (TA) are characteristic and virtually omnipresent surface components of Gram-positive bacteria. They consist of alternating phosphate and polyol (ribitol or glycerol) moieties. Teichoic acids occur in two major forms, lipoteichoic acids (LTA), which are linked to the cell membrane via a membrane-spanning lipid anchor, and wall teichoic acids (WTA), which are covalently linked to peptidoglycan [70]. Extracellular TA are loosely attached to the cell surface and may originate from WTA that have lost covalent anchoring. The structure of cell wall and extracellular TA of *S. epidermidis* have been analyzed in detail [71]. They consist of poly(glycerol phosphate) units, which are substituted at the 2-position of glycerol with alpha-glucose, alpha-glucosamine, D-alanine, or alpha-6-D-alanyl-glucose. Reports on “lipid S”, an alleged pro-inflammatory short-chain form of LTA in *S. epidermidis* [72], are most likely erroneous and caused by co-purification and misinterpretation of mass spectra originating from a phenol-soluble modulin peptide (PSM-mec) present in MRSE [73].

TA have multiple roles in staphylococcal physiology and pathogenesis, contributing to adhesion, colonization, and inflammation [74–76]. In *S. epidermidis*, TA were shown to enhance adhesion to fibronectin [77]. Furthermore, recent research substantiated the long suspected role of WTA in *S. epidermidis* biofilm formation by analyzing a *tagO* mutant of *S. epidermidis* that exhibited decreased attachment and aggregation phenotypes [78]. A direct role of TA in immune evasion of *S. epidermidis* has not yet been evaluated, but as a component that has a significant impact on biofilm formation, TA can be assumed to have such a function. Furthermore, *S. epidermidis* also contains the genes for D-alanylation of TA, a modification that is known from a series of other bacteria, including *S. aureus*, to protect from the activity of AMPs [79]. These genes, together with others that encode AMP protection systems, namely the VraFG transporter and the phospholipid lysylation enzyme MprF [80,81], are regulated by a system that senses AMP presence and was discovered in *S. epidermidis* [82].

Accumulation-associated protein (Aap): In 1997, Hussain et al. described a 140-kilodalton extracellular protein that is essential for the accumulation of *S. epidermidis* on surfaces [83]. This protein was called accumulation-associated protein (Aap). Aap was later shown to form polymeric fibrils on the surface of *S. epidermidis* cells, also mediating intercellular adhesion [84]. One subpopulation of cells expresses fibrils, while another does not. The mechanism underlying this specification is not known. The formation of fibrils is zinc-dependent and proceeds via dimerization of so-called G5 domains and modular association of tandem G5 domains [85]. This mechanism is analogous to that involved in the formation of mammalian cadherin domains. Of note, Aap needs proteolytic processing to obtain its biofilm-active form [86]. In addition to mediating intercellular adhesion and adhesion to surfaces, Aap has also recently been shown to attach *S. epidermidis* to human corneocytes via its terminal A domain [87]. Aap is considered the most important factor contributing to protein-dependent (non-PIA-dependent) biofilm formation in *S. epidermidis*.

Embp: The extracellular matrix-binding protein (Embp) is a giant covalently attached surface protein of 1 MDa [41]. A truncated form of 460 kDa is necessary and sufficient to promote protein-dependent biofilm formation of *S. epidermidis* [88]. In addition, Embp mediates adherence to fibronectin and is thus involved in both adhesion and accumulation stages of biofilm formation [41,88].

Bap/Bhp: The biofilm-associated protein (Bap) is a 239 kDa surface protein involved in biofilm adhesion and accumulation [89]. While in *S. aureus*, Bap is present only in a minority of bovine mastitis isolates, located on a pathogenicity island, it is found frequently in *S. epidermidis* strains [90]. A protein with high similarity to Bap, the Bap homologue protein Bhp, occurs in some *S. epidermidis* strains, but does not appear to be essential for biofilm formation [91].

Structuring and detachment: PSMs. While molecular mechanisms contributing to aggregation during biofilm development have been intensely studied, we lack knowledge about cell-cell disruptive mechanisms. These are required for the formation of the characteristic biofilm structure with fluid-filled channels and mushroom-shaped cellular aggregations, and for the detachment of cells from a biofilm, which controls biofilm thickness and expansion. In several bacteria, including *S. aureus* and *S. epidermidis*, quorum-sensing systems have been implicated in the control of biofilm thickness and biofilm structuring [92–96]. However, the quorum-sensing controlled factors involved in those processes on a mechanistic level have remained largely undefined. In *P. aeruginosa* and *B. subtilis*, surfactant molecules with different chemical natures (rhamnolipid and surfactin, respectively) are involved in biofilm structuring [36,35]. In a recent study, the PSMβ peptides of *S. epidermidis* were shown to structure *S. epidermidis* biofilms and thus fulfill a task similar to that accomplished by rhamnolipid in *P. aeruginosa* [34]. Of note, in that study it was demonstrated for the first time, using the PSMβ peptides of *S. epidermidis* and a murine device-related infection model, that biofilm structuring molecules trigger the dissemination of biofilm-associated infection. Isogenic *S. epidermidis psm*β deletion mutants showed significantly less systemic dissemination from the biofilm and anti-PSMβ antibodies blocked dissemination.

4.1.3 *S. epidermidis* biofilms have a specific, protective gene expression profile—Biofilms represent a strongly divergent mode of growth compared to that of free-floating (often called “planktonic”) bacteria, a situation that for many bacteria is encountered almost exclusively under laboratory conditions. Not surprisingly, gene expression profiles of biofilms show considerable differences when compared to planktonic bacteria in whole genome expression experiments using microarrays. In *S. epidermidis*, similar to other bacteria, gene expression in biofilms is characterized by a suppression of

many active cell processes and an adaptation of metabolic processes to fermentative growth [27]. However, very specific adaptations were also observed. These comprised down-regulation of the Agr (accessory gene regulator) system and the Agr-controlled PSM peptides, which as discussed above were recently attributed a key role in biofilm development [34]. In addition, there was increased expression of genes encoding the biosynthetic machinery for production of the protective surface polymer poly-γ-glutamic acid PGA (see below), exemplifying that over-expression of protective factors not directly involved in aggregation may also contribute to the increased protective characteristics of biofilms.

4.2. Poly-γ-glutamic acid (PGA)

Poly-γ-glutamic acid (PGA) is a linear homopolymer of glutamic acid residues that are linked via the γ-carboxy group of glutamic acid [97]. Thus, it is strictly speaking a peptoid. PGA is found in many microorganisms, in particular in halophilic bacteria, where it is assumed to play a role in osmoprotection [98]. Until its discovery in *S. epidermidis* in 2005 [99], *Bacillus anthracis* was the only pathogenic organism in which PGA was attributed a role in immune evasion, namely in protecting from phagocytosis [100].

In *S. epidermidis*, PGA is composed of a roughly equal amount of D- and L-glutamic acid, while in *B. anthracis*, PGA is composed entirely of D-glutamic acid residues [99]. However, all forms of PGA (100% D-glutamic acid, 100% L-glutamic acid, and mixed) are found in different organisms in nature. Using isogenic deletion mutants in the *cap* locus of *S. epidermidis*, which encodes the PGA biosynthesis genes and is similar to the *cap* locus of *B. anthracis*, PGA of *S. epidermidis* was shown to protect from AMPs, neutrophil killing, and virulence in a mouse model of device-related infection [99]. Of note, while PIA and TA exhibit at least part of their role in protecting from host defenses via their contribution to biofilm formation, PGA did not have a detectable role in biofilm formation [99].

4.3 Toxins in *S. epidermidis*

S. epidermidis is a bacterial species that is commonly described as relatively innocuous, which is in part due to the notion that it lacks secreted toxins – in stark contrast to its aggressive cousin *S. aureus*, whose virulence is based on a large repertoire of secreted molecules that are toxic to humans, such as α-toxin, enterotoxins, and a series of leukocidins [101]. There are reports that describe the sporadic occurrence of toxic shock syndrome toxin (TSST) and enterotoxins in CNS including *S. epidermidis* [102,103]. Recently, a pathogenicity island, termed SePI, has been found and sequenced in one clinical *S. epidermidis* strain [104]. This island contains staphylococcal enterotoxin C3 (SEC3) and staphylococcal enterotoxin-like toxin L (SElL). However, the production of such toxins by *S. epidermidis* has to be regarded as exceptional and the acquisition of toxin gene-harboring MGEs, likely from *S. aureus*, as extremely rare. Possibly, this is due to the presence of so-called CRISPR sequences that appear to be common to *S. epidermidis* while they are absent from *S. aureus* [105]. These genetic elements provide a system that allows distinguishing between self and non-self DNA and the destruction of intruding foreign DNA sequences, such as phages. The mechanism of CRISPR interference has been studied intensively using *S. epidermidis* as a model organism [105].

4.3.1 Phenol-soluble modulins (PSMs)—Recently, the notion that *S. epidermidis* and other CNS are virtually toxin-free had to be somewhat revised with the identification and characterization of the PSMs, a family of genome-encoded peptides with frequently cytolytic character. The term phenol-soluble modulins was coined by the group of S. Klebanoff in 1999, when they described a peptide “complex” withb several pro-inflammatory activities that was purified from *S. epidermidis* culture filtrate using hot

phenol extraction [106]. The PSM "complex", which was then shown to comprise three components, δ-toxin and the newly described PSMα and PSMβ, activated the HIV1-long terminal repeat (LTR), induced cytokine release, activated nuclear factor B in cells of macrophage lineage [106], primed neutrophils and activated the neutrophil oxidative burst [107]. The same group also reported the pro-inflammatory activities of the PSM "complex" to be mediated via the Toll-like receptor 2 (TLR2) [108]. However, this was never substantiated using synthetic peptides or isogenic deletion mutants of *psm* genes, leaving the possibility that TLR2 induction may have been due, at least in part, to co-purified pro-inflammatory impurities. This is even more likely given the recent identification of the formyl peptide receptor 2 (FPR2) as a receptor that binds PSMs and triggers inflammatory responses to PSMs [109]. It still needs to be investigated whether TLR2 is involved in PSM pro-inflammatory activities using *psm* deletion mutants and pure PSM peptides.

Members of the PSM peptide family show distinct physico-chemical characteristics [110–112]. All PSMs contain an amphipatic α-helix that confers surfactant-like properties. The shorter α-type PSMs are about 20–25 amino acids in length with the amphipathic α-helix stretching over the entire peptide. β-type PSMs are about double in size with the C-terminal part containing the α-helix. These characteristics also cause an unusual behavior of PSMs during reversed-phase chromatography compared to all other proteins found in culture filtrate, namely elution at extremely high percentages of organic solvent. This, together with the fact that concentrations of PSMs in culture filtrates are commonly very high, allowed the relatively easy detection of PSMs in several CNS [111]. In *S. epidermidis*, all genetic loci coding for PSMs detected by reversed-phase HPLC/mass spectrometry have been identified either using the detected masses or further purification and N-terminal amino acid sequencing [27,106,113] (Fig. 2). In addition to the 3 PSMs described by Mehlin et al., *S. epidermidis* was found to contain 3 additional PSMs: 2 α-type PSMs (PSMδ, PSMε) and an additional β-type PSM, which is now called PSMβ1, while the original PSMβ is now called PSMβ1. The *S. epidermidis* PSMs are encoded in 4 different genetic loci on the *S. epidermidis* chromosome: The genes coding for PSMα and PSMδ form an operon as do those coding for PSMβ1 and PSMβ2. Interestingly, the *psm*β locus also contains a gene for an additional β-type PSM, which however was never found to be produced [110]. Furthermore, the gene coding for PSMβ1 is found in 2 copies in some *S. epidermidis* strains [34]. The δ-toxin (gene name *hld*) is encoded within RNAIII, the regulatory RNA of the Agr quorum-sensing system, similar to *S. aureus* and other staphylococci. The gene coding for PSMε is not linked to another *psm* gene. Of note, all PSMs are under strict regulation by Agr [113]. In addition to the aforementioned PSMs, a PSM, PSM-mec, was recently discovered on the staphylococcal cassette chromosomes (SCC) mec of types II, III, and VIII, which contain the genes responsible for resistance to methicillin [73]. As many clinical *S. epidermidis* isolates are MRSE and belong to one of those SCCmec types, PSM-mec production is frequent among *S. epidermidis* strains isolated from infection. PSM-mec significantly contributes to virulence in *S. aureus* strains that show relatively high production of that peptide [73]. The role of PSM-mec in virulence of *S. epidermidis* has not yet been investigated directly.

The PSM pattern is characteristic for a given staphylococcal species, with different species producing different PSM peptides and only occasionally occurring significant amino acid sequence similarity between PSMs from different species. For example, the δ-toxin of *S. epidermidis* is only different from that of *S. aureus* in 2 amino acids [114], suggesting a common ancestor. Similarity is also found among the PSMβ peptides of different species. PSMβ peptides were frequently annotated in staphylococcal genomes, including those of *S. epidermidis* that have been sequenced [115,116], whereas the shorter α-type PSMs usually missed the threshold for minimal length of open reading frames. Of note, PSMs lack a signal

peptide and are therefore secreted as the primary translation product, harboring an N-terminal N-formyl methionine. The mechanism of PSM secretion is unknown.

The earlier reports on *S. epidermidis* PSMs passed without much appreciation by the staphylococcal research community, possibly because the pro-inflammatory capacities of PSMs were not further substantiated using deletion mutants and there was no evaluation of the impact that PSMs have on staphylococcal infection. This changed when PSMα peptides were discovered in *S. aureus* and recognized as key contributors to virulence in bacteremia and skin infection caused by community-associated methicillin-resistant *S. aureus* (CA-MRSA) [112]. In particular, *S. aureus* PSMα peptides were demonstrated to exhibit a strong capacity to lyse human neutrophils and other cell types. Mechanistically, there is evidence indicating that the cytolytic capacities of PSMs are not receptor-mediated, but likely caused by their surfactant characteristics [109].

The capacities of *S. epidermidis* PSM peptides to lyse neutrophils and erythrocytes have only recently been analyzed [110]. Similar to *S. aureus* PSMβ peptides, the PSMβ peptides of *S. epidermidis* are not cytolytic, indicating that the lack of cytolytic capacity may be a common feature of the β-type class of PSMs. Most α-type PSMs of *S. epidermidis* have low to moderate cytolytic activities with the notable exception of PSMδ, which reaches a cytolytic capacity comparable to that of the strongly cytolytic *S. aureus* PSMα3 [110].

The discovery that PSMδ is strongly cytolytic to human neutrophils and erythrocytes is of special importance, as it represents the first strongly potent toxin to be discovered in *S. epidermidis* that is conserved in all known members of the species. However, so far, PSMδ was found to be produced only at relatively low levels [110], in accordance with the commonly low overall aggressiveness of *S. epidermidis* as a colonizer and opportunistic pathogen. Possibly, the low production of cytolytic PSMs in *S. epidermidis* is linked to the much lower resistance of *S. epidermidis* compared to *S. aureus* against killing by human neutrophils. A detailed investigation of the contribution of *S. epidermidis* PSMs to infection has not yet been performed, mostly due to the fact that isogenic deletion mutants are difficult to produce in clinical *S. epidermidis* strains and have not yet been constructed except for the *psm*β genes.

4.4. Exoenzymes

Several enzymes that *S. epidermidis* secretes have been implicated in virulence. *S. epidermidis* produces a series of secreted proteases, all of which may contribute to virulence via the destruction of host tissue and host proteins. Specific mechanisms could be attributed to SepA, which degrades human AMPs [117], and Esp, which degrades fibrinogen and complement factor C5 [118]. Esp may also contribute to interspecies interference during colonization (see below) [119]. The roles that secreted lipase plays are poorly understood [120,121]. Finally, *S. epidermidis* secretes a fatty acid-modifying enzyme activity (FAME), which detoxifies fatty acids that are harmful to bacteria [122,120,121]. The proteins or genes responsible for FAME activity are not known.

4.5 Competition with *S. aureus*

It has been speculated for a long time that colonization with *S. epidermidis* prevents overgrowth of the more aggressive *S. aureus* and thus, *S. aureus* infection, which is linked to *S. aureus* colonization [123]. However, evidence for such interference was not available. When cross-interfering quorum-sensing pheromones were discovered in staphylococci [124], notably including *S. epidermidis* pheromones that inhibited quorum-sensing activity of *S. aureus* [125], it was believed that quorum-sensing cross-inhibition could be the source

for a potential *S. epidermidis/S. aureus* interference. However, this could not be verified in vivo [126].

Recently, Iwase et al. reported that *S. epidermidis* strains that express a certain secreted protease prevent nasal colonization with *S. aureus* [119]. In contrast, *S. epidermidis* lacking expression of that previously well characterized protease [118], termed Esp, do not interfere with *S. aureus* in vivo. The underlying mechanism was described as protease-dependent destruction of biofilms. While Esp showed such activity in vitro, it is debatable whether the observed in vivo phenomenon of interspecies competition is due to that mechanism [127]. Nevertheless, this study clearly demonstrated that interspecies competition between *S. aureus* and *S. epidermidis* exists in the nares and is, at least in part, responsible for the observed individual differences in nasal colonization with *S. aureus*.

4.6 Are there virulence factors in *S. epidermidis* that distinguish invasive from commensal strains?

It has been noted that the aggressiveness of *S. aureus* and the relatively benign relationship that *S. epidermidis* has with its host allows the two organisms to survive and spread, each by using a different approach [128]. The *S. epidermidis* approach would consist of a series of "passive" mechanisms to evade host defenses, such as the production of protective matrix polymers, without the production of aggressive toxins. This notion has been largely confirmed with the recent more thorough investigation of *S. epidermidis* virulence mechanisms. Interestingly, despite the discovery of PSMs as a series of novel potentially aggressive toxins in *S. epidermidis*, a detailed look at PSM expression in *S. epidermidis* confirmed rather than negated that notion: the expression pattern of PSM peptides is clearly shifted, compared to *S. aureus*, to those that lack cytolytic activity, such as the PSMβ peptides [110].

It has become clear that no virulence mechanism exists in *S. epidermidis* that clearly distinguishes invasive from colonizing strains. In a study using comparative genomic hybridization, a genome-wide comparison of strains isolated from infections of prostheses versus strains from healthy individuals, no factor could be identified that was solely present in infectious strains, but absent from control strains [129]. Nevertheless, several studies confirmed the in average more frequent presence of the *ica* genes encoding PIA synthesis and the insertion element IS256 in invasive strains [130–133]. These studies underscored the importance of PIA in infection and suggested that IS256 may contribute to genetic adaptations allowing optimization of gene content and expression to an infectious lifestyle. Insertion of IS256 was shown for example to occur in the *ica* operon, abolishing PIA synthesis [134]. Furthermore, a study with human volunteers indicated that *ica*-positive strains are less adapted to colonization [135]. Moreover, strains belonging to ST2, the by far most frequently found clonal type of hospital-associated invasive *S. epidermidis*, are all *ica*- and IS256-positive [132,136]. Then again, it has also been pointed out that when using higher stringency controls, *ica* and other virulence genes are not correlated with invasiveness [137]. Taken together, these studies indicate that there are no genetic markers that can be used to clearly predict the aggressiveness of *S. epidermidis* strains. In further support of that notion, the detailed investigation of virulence mechanisms of *S. epidermidis* in recent years has indicated that most if not all virulence factors in that bacterium have original roles in its commensal lifestyle. Likely, PSMs, PIA and other biofilm factors all have such original roles in establishing growth and allowing survival in microbial agglomerations on the skin [138].

As a consequence, any therapeutic directed against *S. epidermidis* virulence factors would also target commensal strains. Any such therapeutic would have to be evaluated for its impact on *S. epidermidis* colonization and its role in controlling the composition of the

human microflora, especially in light of the recent findings regarding *S. epidermidis*-*S. aureus* interference.

Acknowledgments

This work was supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

References

1. Kloos WE, Musselwhite MS. Distribution and persistence of *Staphylococcus* and *Micrococcus* species and other aerobic bacteria on human skin. Appl Microbiol. 1975; 30(3):381–385. [PubMed: 810086]
2. Grice EA, Segre JA. The skin microbiome. Nat Rev Microbiol. 2011; 9(4):244–253. doi:10.1038/nrmicro2537. [PubMed: 21407241]
3. Kloos, W.; Schleifer, KH. Staphylococcus. In: PHA, S.; S, M.; ME, S.; JG, H., editors. Bergey's Manual of Systematic Bacteriology. Williams & Wilkins; Baltimore: 1986.
4. Rogers KL, Fey PD, Rupp ME. Coagulase-negative staphylococcal infections. Infect Dis Clin North Am. 2009; 23(1):73–98. [PubMed: 19135917]
5. Etienne J, Pangon B, Leport C, Wolff M, Clair B, Perronne C, Brun Y, Bure A. *Staphylococcus lugdunensis* endocarditis. Lancet. 1989; 1(8634):390. [PubMed: 2563548]
6. Zinkernagel AS, Zinkernagel MS, Elzi MV, Genoni M, Gubler J, Zbinden R, Mueller NJ. Significance of *Staphylococcus lugdunensis* bacteremia: report of 28 cases and review of the literature. Infection. 2008; 36(4):314–321. [PubMed: 18648747]
7. Lina, G.; Etienne, J.; Vandenesch, F. Biology and pathogenicity of staphylococci other than *Staphylococcus aureus* and *Staphylococcus epidermidis*. In: Fischetti, VA.; Novick, RP.; J.J., F.; Portnoy, DA.; Rood, JI., editors. Gram-positive pathogens. ASM Press; Washington, DC: 2000.
8. O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, Masur H, McCormick RD, Mermel LA, Pearson ML, Raad II, Randolph A, Weinstein RA. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recomm Rep. 2002; 51(RR-10):1–29. [PubMed: 12233868]
9. Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. Lancet Infect Dis. 2007; 7(10):645–657. [PubMed: 17897607]
10. Wang A, Athan E, Pappas PA, Fowler VG Jr. Olaison L, Pare C, Almirante B, Munoz P, Rizzi M, Naber C, Logar M, Tattevin P, Iarussi DL, Selton-Suty C, Jones SB, Casabe J, Morris A, Corey GR, Cabell CH. Contemporary clinical profile and outcome of prosthetic valve endocarditis. Jama. 2007; 297(12):1354–1361. [PubMed: 17392239]
11. Cheung GY, Otto M. Understanding the significance of *Staphylococcus epidermidis* bacteremia in babies and children. Curr Opin Infect Dis. 2010 doi:10.1097/QCO.0b013e328337fecb.
12. Anday EK, Talbot GH. Coagulase-negative *Staphylococcus* bacteremia--a rising threat in the newborn infant. Ann Clin Lab Sci. 1985; 15(3):246–251. [PubMed: 3994294]
13. Diekema DJ, Pfaller MA, Schmitz FJ, Smayevsky J, Bell J, Jones RN, Beach M. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997–1999. Clin Infect Dis. 2001; 32(Suppl 2):S114–132. [PubMed: 11320452]
14. Chambers HF, Hartman BJ, Tomasz A. Increased amounts of a novel penicillin-binding protein in a strain of methicillin-resistant *Staphylococcus aureus* exposed to nafcillin. J Clin Invest. 1985; 76(1):325–331. [PubMed: 4019783]
15. Tomasz A, Nachman S, Leaf H. Stable classes of phenotypic expression in methicillin-resistant clinical isolates of staphylococci. Antimicrob Agents Chemother. 1991; 35(1):124–129. [PubMed: 2014967]
16. Jones RN. Microbiological features of vancomycin in the 21st century: minimum inhibitory concentration creep, bactericidal/static activity, and applied breakpoints to predict clinical

outcomes or detect resistant strains. Clin Infect Dis. 2006; 42(Suppl 1):S13–24. [PubMed: 16323115]

17. Costerton JW, Lewandowski Z, Caldwell DE, Korber DR, Lappin-Scott HM. Microbial biofilms. Annu Rev Microbiol. 1995; 49:711–745. [PubMed: 8561477]
18. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science. 1999; 284(5418):1318–1322. [PubMed: 10334980]
19. Leid JG, Shirtliff ME, Costerton JW, Stoodley AP. Human leukocytes adhere to, penetrate, and respond to *Staphylococcus aureus* biofilms. Infect Immun. 2002; 70(11):6339–6345. [PubMed: 12379713]
20. Thurlow LR, Hanke ML, Fritz T, Angle A, Aldrich A, Williams SH, Engebretsen IL, Bayles KW, Horswill AR, Kielian T. *Staphylococcus aureus* biofilms prevent macrophage phagocytosis and attenuate inflammation in vivo. J Immunol. 2011; 186(11):6585–6596. [PubMed: 21525381]
21. Mah TF, O'Toole GA. Mechanisms of biofilm resistance to antimicrobial agents. Trends Microbiol. 2001; 9(1):34–39. [PubMed: 11166241]
22. Walters MC 3rd, Roe F, Bugnicourt A, Franklin MJ, Stewart PS. Contributions of antibiotic penetration, oxygen limitation, and low metabolic activity to tolerance of Pseudomonas aeruginosa biofilms to ciprofloxacin and tobramycin. Antimicrob Agents Chemother. 2003; 47(1):317–323. [PubMed: 12499208]
23. Leite B, Gomes F, Teixeira P, Souza C, Pizzolitto E, Oliveira R. In vitro activity of daptomycin, linezolid and rifampicin on *Staphylococcus epidermidis* biofilms. Curr Microbiol. 2011; 63(3): 313–317. [PubMed: 21761219]
24. Dunne WM Jr. Mason EO Jr. Kaplan SL. Diffusion of rifampin and vancomycin through a *Staphylococcus epidermidis* biofilm. Antimicrob Agents Chemother. 1993; 37(12):2522–2526. [PubMed: 8109913]
25. Keren I, Kaldalu N, Spoering A, Wang Y, Lewis K. Persister cells and tolerance to antimicrobials. FEMS Microbiol Lett. 2004; 230(1):13–18. [PubMed: 14734160]
26. Shapiro JA, Nguyen VL, Chamberlain NR. Evidence for persisters in *Staphylococcus epidermidis* RP62a planktonic cultures and biofilms. J Med Microbiol. 2011; 60(Pt 7):950–960. [PubMed: 21415203]
27. Yao Y, Sturdevant DE, Otto M. Genomewide analysis of gene expression in *Staphylococcus epidermidis* biofilms: insights into the pathophysiology of *S. epidermidis* biofilms and the role of phenol-soluble modulins in formation of biofilms. J Infect Dis. 2005; 191(2):289–298. [PubMed: 15609240]
28. Rodgers J, Phillips F, Olliff C. The effects of extracellular slime from *Staphylococcus epidermidis* on phagocytic ingestion and killing. FEMS Immunol Med Microbiol. 1994; 9(2):109–115. [PubMed: 7804161]
29. Johnson GM, Lee DA, Regelmann WE, Gray ED, Peters G, Quie PG. Interference with granulocyte function by *Staphylococcus epidermidis* slime. Infect Immun. 1986; 54(1):13–20. [PubMed: 3019888]
30. Noble MA, Reid PE, Park CM, Chan VY. Inhibition of human neutrophil bacteriocidal activity by extracellular substance from slime-producing *Staphylococcus epidermidis*. Diagn Microbiol Infect Dis. 1986; 4(4):335–339. [PubMed: 3698545]
31. Kristian SA, Birkenstock TA, Sauder U, Mack D, Gotz F, Landmann R. Biofilm formation induces C3a release and protects *Staphylococcus epidermidis* from IgG and complement deposition and from neutrophil-dependent killing. J Infect Dis. 2008; 197(7):1028–1035. [PubMed: 18419540]
32. Otto M. Bacterial evasion of antimicrobial peptides by biofilm formation. Curr Top Microbiol Immunol. 2006; 306:251–258. [PubMed: 16909925]
33. O'Toole G, Kaplan HB, Kolter R. Biofilm formation as microbial development. Annu Rev Microbiol. 2000; 54:49–79. [PubMed: 11018124]
34. Wang R, Khan BA, Cheung GY, Bach TH, Jameson-Lee M, Kong KF, Queck SY, Otto M. *Staphylococcus epidermidis* surfactant peptides promote biofilm maturation and dissemination of biofilm-associated infection in mice. J Clin Invest. 2011; 121(1):238–248. [PubMed: 21135501]
35. Boles BR, Thoendel M, Singh PK. Rhamnolipids mediate detachment of *Pseudomonas aeruginosa* from biofilms. Mol Microbiol. 2005; 57(5):1210–1223. [PubMed: 16101996]

36. Branda SS, Gonzalez-Pastor JE, Ben-Yehuda S, Losick R, Kolter R. Fruiting body formation by *Bacillus subtilis*. Proc Natl Acad Sci U S A. 2001; 98(20):11621–11626. [PubMed: 11572999]
37. Foster TJ, Hook M. Surface protein adhesins of *Staphylococcus aureus*. Trends Microbiol. 1998; 6(12):484–488. [PubMed: 10036727]
38. Bowden MG, Chen W, Singvall J, Xu Y, Peacock SJ, Valtulina V, Speziale P, Hook M. Identification and preliminary characterization of cell-wall-anchored proteins of *Staphylococcus epidermidis*. Microbiology. 2005; 151(Pt 5):1453–1464. [PubMed: 15870455]
39. Davis SL, Gurusiddappa S, McCrea KW, Perkins S, Hook M. SdrG, a fibrinogen-binding bacterial adhesin of the microbial surface components recognizing adhesive matrix molecules subfamily from *Staphylococcus epidermidis*, targets the thrombin cleavage site in the Bbeta chain. J Biol Chem. 2001; 276(30):27799–27805. [PubMed: 11371571]
40. Hartford O, O'Brien L, Schofield K, Wells J, Foster TJ. The Fbe (SdrG) protein of *Staphylococcus epidermidis* HB promotes bacterial adherence to fibrinogen. Microbiology. 2001; 147(Pt 9):2545–2552. [PubMed: 11535794]
41. Williams RJ, Henderson B, Sharp LJ, Nair SP. Identification of a fibronectin-binding protein from *Staphylococcus epidermidis*. Infect Immun. 2002; 70(12):6805–6810. [PubMed: 12438356]
42. Heilmann C, Hussain M, Peters G, Gotz F. Evidence for autolysin-mediated primary attachment of *Staphylococcus epidermidis* to a polystyrene surface. Mol Microbiol. 1997; 24(5):1013–1024. [PubMed: 9220008]
43. Heilmann C, Thumm G, Chhatwal GS, Hartleib J, Uekotter A, Peters G. Identification and characterization of a novel autolysin (Aae) with adhesive properties from *Staphylococcus epidermidis*. Microbiology. 2003; 149(Pt 10):2769–2778. [PubMed: 14523110]
44. Bowden MG, Visai L, Longshaw CM, Holland KT, Speziale P, Hook M. Is the GehD lipase from *Staphylococcus epidermidis* a collagen binding adhesin? J Biol Chem. 2002; 277(45):43017–43023. [PubMed: 12218064]
45. Mazmanian SK, Liu G, Ton-That H, Schneewind O. *Staphylococcus aureus* sortase, an enzyme that anchors surface proteins to the cell wall. Science. 1999; 285(5428):760–763. [PubMed: 10427003]
46. Heilmann C. Adhesion mechanisms of staphylococci. Adv Exp Med Biol. 2011; 715:105–123. [PubMed: 21557060]
47. Mack D, Fischer W, Krokotsch A, Leopold K, Hartmann R, Egge H, Laufs R. The intercellular adhesin involved in biofilm accumulation of *Staphylococcus epidermidis* is a linear beta-1,6-linked glucosaminoglycan: purification and structural analysis. J Bacteriol. 1996; 178(1):175–183. [PubMed: 8550413]
48. Heilmann C, Schweitzer O, Gerke C, Vanittanakom N, Mack D, Gotz F. Molecular basis of intercellular adhesion in the biofilm-forming *Staphylococcus epidermidis*. Mol Microbiol. 1996; 20(5):1083–1091. [PubMed: 8809760]
49. Conlon KM, Humphreys H, O'Gara JP. Regulation of *icaR* gene expression in *Staphylococcus epidermidis*. FEMS Microbiol Lett. 2002; 216(2):171–177. [PubMed: 12435499]
50. Conlon KM, Humphreys H, O'Gara JP. *icaR* encodes a transcriptional repressor involved in environmental regulation of *ica* operon expression and biofilm formation in *Staphylococcus epidermidis*. J Bacteriol. 2002; 184(16):4400–4408. [PubMed: 12142410]
51. Jefferson KK, Pier DB, Goldmann DA, Pier GB. The teicoplanin-associated locus regulator (TcaR) and the intercellular adhesin locus regulator (IcaR) are transcriptional inhibitors of the *ica* locus in *Staphylococcus aureus*. J Bacteriol. 2004; 186(8):2449–2456. [PubMed: 15060048]
52. Handke LD, Slater SR, Conlon KM, O'Donnell ST, Olson ME, Bryant KA, Rupp ME, O'Gara JP, Fey PD. SigmaB and SarA independently regulate polysaccharide intercellular adhesin production in *Staphylococcus epidermidis*. Can J Microbiol. 2007; 53(1):82–91. [PubMed: 17496953]
53. Li M, Villaruz AE, Vadyvaloo V, Sturdevant DE, Otto M. AI-2-dependent gene regulation in *Staphylococcus epidermidis*. BMC Microbiol. 2008; 8:4. [PubMed: 18182108]
54. Vuong C, Gerke C, Somerville GA, Fischer ER, Otto M. Quorum-sensing control of biofilm factors in *Staphylococcus epidermidis*. J Infect Dis. 2003; 188(5):706–718. [PubMed: 12934187]
55. Gerke C, Kraft A, Sussmuth R, Schweitzer O, Gotz F. Characterization of the N-acetylglucosaminyltransferase activity involved in the biosynthesis of the *Staphylococcus*

epidermidis polysaccharide intercellular adhesin. J Biol Chem. 1998; 273(29):18586–18593. [PubMed: 9660830]

56. Vuong C, Kocianova S, Voyich JM, Yao Y, Fischer ER, DeLeo FR, Otto M. A crucial role for exopolysaccharide modification in bacterial biofilm formation, immune evasion, and virulence. J Biol Chem. 2004; 279(52):54881–54886. [PubMed: 15501828]
57. Maira-Litran T, Kropec A, Goldmann DA, Pier GB. Comparative opsonic and protective activities of *Staphylococcus aureus* conjugate vaccines containing native or deacetylated Staphylococcal Poly-N-acetyl-beta-(1–6)-glucosamine. Infect Immun. 2005; 73(10):6752–6762. [PubMed: 16177353]
58. Mack D, Haeder M, Siemssen N, Laufs R. Association of biofilm production of coagulase-negative staphylococci with expression of a specific polysaccharide intercellular adhesin. J Infect Dis. 1996; 174(4):881–884. [PubMed: 8843236]
59. Kogan G, Sadovskaya I, Chaignon P, Chokr A, Jabbouri S. Biofilms of clinical strains of *Staphylococcus* that do not contain polysaccharide intercellular adhesin. FEMS Microbiol Lett. 2006; 255(1):11–16. [PubMed: 16436056]
60. Rohde H, Burandt EC, Siemssen N, Frommelt L, Burdelski C, Wurster S, Scherpe S, Davies AP, Harris LG, Horstkotte MA, Knobloch JK, Ragunath C, Kaplan JB, Mack D. Polysaccharide intercellular adhesin or protein factors in biofilm accumulation of *Staphylococcus epidermidis* and *Staphylococcus aureus* isolated from prosthetic hip and knee joint infections. Biomaterials. 2007; 28(9):1711–1720. [PubMed: 17187854]
61. Mack D, Riedewald J, Rohde H, Magnus T, Feucht HH, Elsner HA, Laufs R, Rupp ME. Essential functional role of the polysaccharide intercellular adhesin of *Staphylococcus epidermidis* in hemagglutination. Infect Immun. 1999; 67(2):1004–1008. [PubMed: 9916125]
62. Stevens NT, Sadovskaya I, Jabbouri S, Sattar T, O'Gara JP, Humphreys H, Greene CM. *Staphylococcus epidermidis* polysaccharide intercellular adhesin induces IL-8 expression in human astrocytes via a mechanism involving TLR2. Cell Microbiol. 2009; 11(3):421–432. [PubMed: 19016779]
63. Vuong C, Otto M. The biofilm exopolysaccharide polysaccharide intercellular adhesin--a molecular and biochemical approach. Methods Mol Biol. 2008; 431:97–106. [PubMed: 18287750]
64. Rupp ME, Fey PD, Heilmann C, Gotz F. Characterization of the importance of *Staphylococcus epidermidis* autolysin and polysaccharide intercellular adhesin in the pathogenesis of intravascular catheter-associated infection in a rat model. J Infect Dis. 2001; 183(7):1038–1042. [PubMed: 11237828]
65. Rupp ME, Ulphani JS, Fey PD, Bartscht K, Mack D. Characterization of the importance of polysaccharide intercellular adhesin/hemagglutinin of *Staphylococcus epidermidis* in the pathogenesis of biomaterial-based infection in a mouse foreign body infection model. Infect Immun. 1999; 67(5):2627–2632. [PubMed: 10225932]
66. Rupp ME, Ulphani JS, Fey PD, Mack D. Characterization of *Staphylococcus epidermidis* polysaccharide intercellular adhesin/hemagglutinin in the pathogenesis of intravascular catheter-associated infection in a rat model. Infect Immun. 1999; 67(5):2656–2659. [PubMed: 10225938]
67. Begun J, Gaiani JM, Rohde H, Mack D, Calderwood SB, Ausubel FM, Sifri CD. Staphylococcal biofilm exopolysaccharide protects against *Caenorhabditis elegans* immune defenses. PLoS Pathog. 2007; 3(4):e57. [PubMed: 17447841]
68. Kristian SA, Golda T, Ferracin F, Cramton SE, Neumeister B, Peschel A, Gotz F, Landmann R. The ability of biofilm formation does not influence virulence of *Staphylococcus aureus* and host response in a mouse tissue cage infection model. Microb Pathog. 2004; 36(5):237–245. [PubMed: 15043859]
69. Chokr A, Leterme D, Watier D, Jabbouri S. Neither the presence of *ica* locus, nor in vitro-biofilm formation ability is a crucial parameter for some *Staphylococcus epidermidis* strains to maintain an infection in a guinea pig tissue cage model. Microb Pathog. 2007; 42(2–3):94–97. [PubMed: 17084581]
70. Glaser L. Bacterial cell surface polysaccharides. Annu Rev Biochem. 1973; 42:91–112. [PubMed: 4147186]

71. Sadovskaya I, Vinogradov E, Li J, Jabbouri S. Structural elucidation of the extracellular and cell-wall teichoic acids of *Staphylococcus epidermidis* RP62A, a reference biofilm-positive strain. Carbohydr Res. 2004; 339(8):1467–1473. [PubMed: 15178389]
72. Lambert PA, Worthington T, Tebbs SE, Elliott TS. Lipid S, a novel *Staphylococcus epidermidis* exocellular antigen with potential for the serodiagnosis of infections. FEMS Immunol Med Microbiol. 2000; 29(3):195–202. [PubMed: 11064266]
73. Queck SY, Khan BA, Wang R, Bach TH, Kretschmer D, Chen L, Kreiswirth BN, Peschel A, DeLeo FR, Otto M. Mobile genetic element-encoded cytolysin connects virulence to methicillin resistance in MRSA. PLoS Pathog. 2009; 5(7):e1000533. [PubMed: 19649313]
74. Gross M, Cramton SE, Gotz F, Peschel A. Key role of teichoic acid net charge in *Staphylococcus aureus* colonization of artificial surfaces. Infect Immun. 2001; 69(5):3423–3426. [PubMed: 11292767]
75. Weidenmaier C, Kokai-Kun JF, Kristian SA, Chanturiya T, Kalbacher H, Gross M, Nicholson G, Neumeister B, Mond JJ, Peschel A. Role of teichoic acids in *Staphylococcus aureus* nasal colonization, a major risk factor in nosocomial infections. Nat Med. 2004; 10(3):243–245. [PubMed: 14758355]
76. Weidenmaier C, Peschel A. Teichoic acids and related cell-wall glycopolymers in Gram-positive physiology and host interactions. Nat Rev Microbiol. 2008; 6(4):276–287. [PubMed: 18327271]
77. Hussain M, Heilmann C, Peters G, Herrmann M. Teichoic acid enhances adhesion of *Staphylococcus epidermidis* to immobilized fibronectin. Microb Pathog. 2001; 31(6):261–270. [PubMed: 11747374]
78. Holland LM, Conlon B, O'Gara JP. Mutation of *tagO* reveals an essential role for wall teichoic acids in *Staphylococcus epidermidis* biofilm development. Microbiology. 2011; 157(Pt 2):408–418. [PubMed: 21051486]
79. Peschel A, Otto M, Jack RW, Kalbacher H, Jung G, Gotz F. Inactivation of the *dlt* operon in *Staphylococcus aureus* confers sensitivity to defensins, protegrins, and other antimicrobial peptides. J Biol Chem. 1999; 274(13):8405–8410. [PubMed: 10085071]
80. Li M, Cha DJ, Lai Y, Villaruz AE, Sturdevant DE, Otto M. The antimicrobial peptide-sensing system aps of *Staphylococcus aureus*. Mol Microbiol. 2007; 66(5):1136–1147. [PubMed: 17961141]
81. Peschel A, Jack RW, Otto M, Collins LV, Staubitz P, Nicholson G, Kalbacher H, Nieuwenhuizen WF, Jung G, Tarkowski A, van Kessel KP, van Strijp JA. *Staphylococcus aureus* resistance to human defensins and evasion of neutrophil killing via the novel virulence factor MprF is based on modification of membrane lipids with llysine. J Exp Med. 2001; 193(9):1067–1076. [PubMed: 11342591]
82. Li M, Lai Y, Villaruz AE, Cha DJ, Sturdevant DE, Otto M. Gram-positive three-component antimicrobial peptide-sensing system. Proc Natl Acad Sci U S A. 2007; 104(22):9469–9474. [PubMed: 17517597]
83. Hussain M, Herrmann M, von Eiff C, Perdreau-Remington F, Peters G. A 140-kilodalton extracellular protein is essential for the accumulation of *Staphylococcus epidermidis* strains on surfaces. Infect Immun. 1997; 65(2):519–524. [PubMed: 9009307]
84. Banner MA, Cunniffe JG, Macintosh RL, Foster TJ, Rohde H, Mack D, Hoyes E, Derrick J, Upton M, Handley PS. Localized tufts of fibrils on *Staphylococcus epidermidis* NCTC 11047 are comprised of the accumulation-associated protein. J Bacteriol. 2007; 189(7):2793–2804. [PubMed: 17277069]
85. Conrady DG, Brescia CC, Horii K, Weiss AA, Hassett DJ, Herr AB. A zinc-dependent adhesion module is responsible for intercellular adhesion in staphylococcal biofilms. Proc Natl Acad Sci U S A. 2008; 105(49):19456–19461. [PubMed: 19047636]
86. Rohde H, Burdelski C, Bartscht K, Hussain M, Buck F, Horstkotte MA, Knobloch JK, Heilmann C, Herrmann M, Mack D. Induction of *Staphylococcus epidermidis* biofilm formation via proteolytic processing of the accumulation-associated protein by staphylococcal and host proteases. Mol Microbiol. 2005; 55(6):1883–1895. [PubMed: 15752207]
87. Macintosh RL, Brittan JL, Bhattacharya R, Jenkinson HF, Derrick J, Upton M, Handley PS. The terminal A domain of the fibrillar accumulation-associated protein (Aap) of *Staphylococcus*

epidermidis mediates adhesion to human corneocytes. J Bacteriol. 2009; 191(22):7007–7016. [PubMed: 19749046]

88. Christner M, Franke GC, Schommer NN, Wendt U, Wegert K, Pehle P, Kroll G, Schulze C, Buck F, Mack D, Aepfelbacher M, Rohde H. The giant extracellular matrix-binding protein of *Staphylococcus epidermidis* mediates biofilm accumulation and attachment to fibronectin. Mol Microbiol. 2010; 75(1):187–207. [PubMed: 19943904]
89. Cucarella C, Solano C, Valle J, Amorena B, Lasa I, Penades JR. Bap, a *Staphylococcus aureus* surface protein involved in biofilm formation. J Bacteriol. 2001; 183(9):2888–2896. [PubMed: 11292810]
90. Tormo MA, Knecht E, Gotz F, Lasa I, Penades JR. Bap-dependent biofilm formation by pathogenic species of *Staphylococcus*: evidence of horizontal gene transfer? Microbiology. 2005; 151(Pt 7):2465–2475. [PubMed: 16000737]
91. Lasa I, Penades JR. Bap: a family of surface proteins involved in biofilm formation. Res Microbiol. 2006; 157(2):99–107. [PubMed: 16427771]
92. Davies DG, Parsek MR, Pearson JP, Iglewski BH, Costerton JW, Greenberg EP. The involvement of cell-to-cell signals in the development of a bacterial biofilm. Science. 1998; 280(5361):295–298. [PubMed: 9535661]
93. Yarwood JM, Bartels DJ, Volper EM, Greenberg EP. Quorum sensing in *Staphylococcus aureus* biofilms. J Bacteriol. 2004; 186(6):1838–1850. [PubMed: 14996815]
94. Vuong C, Saenz HL, Gotz F, Otto M. Impact of the *agr* quorum-sensing system on adherence to polystyrene in *Staphylococcus aureus*. J Infect Dis. 2000; 182(6):1688–1693. [PubMed: 11069241]
95. Vuong C, Kocianova S, Yao Y, Carmody AB, Otto M. Increased colonization of indwelling medical devices by quorum-sensing mutants of *Staphylococcus epidermidis* in vivo. J Infect Dis. 2004; 190(8):1498–1505. [PubMed: 15378444]
96. Boles BR, Horswill AR. Agr-mediated dispersal of *Staphylococcus aureus* biofilms. PLoS Pathog. 2008; 4(4):e1000052. [PubMed: 18437240]
97. Ashiuchi M, Misono H. Biochemistry and molecular genetics of poly-gamma-glutamate synthesis. Appl Microbiol Biotechnol. 2002; 59(1):9–14. [PubMed: 12073126]
98. Oppermann-Sanio FB, Steinbuchel A. Occurrence, functions and biosynthesis of polyamides in microorganisms and biotechnological production. Naturwissenschaften. 2002; 89(1):11–22. [PubMed: 12008968]
99. Kocianova S, Vuong C, Yao Y, Voyich JM, Fischer ER, DeLeo FR, Otto M. Key role of poly-gamma-DL-glutamic acid in immune evasion and virulence of *Staphylococcus epidermidis*. J Clin Invest. 2005; 115(3):688–694. [PubMed: 15696197]
100. Makino S, Uchida I, Terakado N, Sasakawa C, Yoshikawa M. Molecular characterization and protein analysis of the *cap* region, which is essential for encapsulation in *Bacillus anthracis*. J Bacteriol. 1989; 171(2):722–730. [PubMed: 2536679]
101. Foster TJ. Immune evasion by staphylococci. Nat Rev Microbiol. 2005; 3(12):948–958. [PubMed: 16322743]
102. Bautista L, Gaya P, Medina M, Nunez M. A quantitative study of enterotoxin production by sheep milk staphylococci. Appl Environ Microbiol. 1988; 54(2):566–569. [PubMed: 3355142]
103. Marin ME, de la Rosa MC, Cornejo I. Enterotoxigenicity of *Staphylococcus* strains isolated from Spanish dry-cured hams. Appl Environ Microbiol. 1992; 58(3):1067–1069. [PubMed: 1575480]
104. Madhusoodanan J, Seo KS, Remortel B, Park JY, Hwang SY, Fox LK, Park YH, Deobald CF, Wang D, Liu S, Daugherty SC, Gill AL, Bohach GA, Gill SR. An Enterotoxin-Bearing Pathogenicity Island in *Staphylococcus epidermidis*. J Bacteriol. 2011; 193(8):1854–1862. [PubMed: 21317317]
105. Marraffini LA, Sontheimer EJ. CRISPR interference limits horizontal gene transfer in staphylococci by targeting DNA. Science. 2008; 322(5909):1843–1845. [PubMed: 19095942]
106. Mehlin C, Headley CM, Klebanoff SJ. An inflammatory polypeptide complex from *Staphylococcus epidermidis*: isolation and characterization. J Exp Med. 1999; 189(6):907–918. [PubMed: 10075974]

107. Liles WC, Thomsen AR, O'Mahony DS, Klebanoff SJ. Stimulation of human neutrophils and monocytes by staphylococcal phenol-soluble modulin. J Leukoc Biol. 2001; 70(1):96–102. [PubMed: 11435491]

108. Hajjar AM, O'Mahony DS, Ozinsky A, Underhill DM, Aderem A, Klebanoff SJ, Wilson CB. Cutting edge: functional interactions between toll-like receptor (TLR) 2 and TLR1 or TLR6 in response to phenol-soluble modulin. J Immunol. 2001; 166(1):15–19. [PubMed: 11123271]

109. Kretschmer D, Gleske AK, Rautenberg M, Wang R, Koberle M, Bohn E, Schoneberg T, Rabiet MJ, Boulay F, Klebanoff SJ, van Kessel KA, van Strijp JA, Otto M, Peschel A. Human formyl peptide receptor 2 senses highly pathogenic *Staphylococcus aureus*. Cell Host Microbe. 2010; 7(6):463–473. [PubMed: 20542250]

110. Cheung GY, Rigby K, Wang R, Queck SY, Braughton KR, Whitney AR, Teintze M, DeLeo FR, Otto M. *Staphylococcus epidermidis* strategies to avoid killing by human neutrophils. PLoS Pathog. 2010; 6(10) doi:10.1371/journal.ppat.1001133.

111. Rautenberg M, Joo HS, Otto M, Peschel A. Neutrophil responses to staphylococcal pathogens and commensals via the formyl peptide receptor 2 relates to phenol-soluble modulin release and virulence. Faseb J. 2011; 25(4):1254–1263. [PubMed: 21183593]

112. Wang R, Braughton KR, Kretschmer D, Bach TH, Queck SY, Li M, Kennedy AD, Dorward DW, Klebanoff SJ, Peschel A, DeLeo FR, Otto M. Identification of novel cytolytic peptides as key virulence determinants for community-associated MRSA. Nat Med. 2007; 13(12):1510–1514. [PubMed: 17994102]

113. Vuong C, Durr M, Carmody AB, Peschel A, Klebanoff SJ, Otto M. Regulated expression of pathogen-associated molecular pattern molecules in *Staphylococcus epidermidis*: quorum-sensing determines pro-inflammatory capacity and production of phenol-soluble modulins. Cell Microbiol. 2004; 6(8):753–759. [PubMed: 15236642]

114. McKevitt AI, Bjornson GL, Mauracher CA, Scheifele DW. Amino acid sequence of a deltalike toxin from *Staphylococcus epidermidis*. Infect Immun. 1990; 58(5):1473–1475. [PubMed: 2323825]

115. Gill SR, Fouts DE, Archer GL, Mongodin EF, Deboy RT, Ravel J, Paulsen IT, Kolonay JF, Brinkac L, Beanan M, Dodson RJ, Daugherty SC, Madupu R, Angiuoli SV, Durkin AS, Haft DH, Vamathevan J, Khouri H, Utterback T, Lee C, Dimitrov G, Jiang L, Qin H, Weidman J, Tran K, Kang K, Hance IR, Nelson KE, Fraser CM. Insights on evolution of virulence and resistance from the complete genome analysis of an early methicillin-resistant *Staphylococcus aureus* strain and a biofilm-producing methicillin-resistant *Staphylococcus epidermidis* strain. J Bacteriol. 2005; 187(7):2426–2438. [PubMed: 15774886]

116. Zhang YQ, Ren SX, Li HL, Wang YX, Fu G, Yang J, Qin ZQ, Miao YG, Wang WY, Chen RS, Shen Y, Chen Z, Yuan ZH, Zhao GP, Qu D, Danchin A, Wen YM. Genome-based analysis of virulence genes in a non-biofilm-forming *Staphylococcus epidermidis* strain (ATCC 12228). Mol Microbiol. 2003; 49(6):1577–1593. [PubMed: 12950922]

117. Lai Y, Villaruz AE, Li M, Cha DJ, Sturdevant DE, Otto M. The human anionic antimicrobial peptide dermcidin induces proteolytic defence mechanisms in staphylococci. Mol Microbiol. 2007; 63(2):497–506. [PubMed: 17176256]

118. Dubin G, Chmiel D, Mak P, Rakwalska M, Rzychon M, Dubin A. Molecular cloning and biochemical characterisation of proteases from *Staphylococcus epidermidis*. Biol Chem. 2001; 382(11):1575–1582. [PubMed: 11767947]

119. Iwase T, Uehara Y, Shinji H, Tajima A, Seo H, Takada K, Agata T, Mizunoe Y. *Staphylococcus epidermidis* Esp inhibits *Staphylococcus aureus* biofilm formation and nasal colonization. Nature. 2010; 465(7296):346–349. [PubMed: 20485435]

120. Farrell AM, Foster TJ, Holland KT. Molecular analysis and expression of the lipase of *Staphylococcus epidermidis*. J Gen Microbiol. 1993; 139(2):267–277. [PubMed: 8436947]

121. Simons JW, van Kampen MD, Riel S, Gotz F, Egmond MR, Verheij HM. Cloning, purification and characterisation of the lipase from *Staphylococcus epidermidis*-comparison of the substrate selectivity with those of other microbial lipases. Eur J Biochem. 1998; 253(3):675–683. [PubMed: 9654065]

122. Chamberlain NR, Brueggemann SA. Characterisation and expression of fatty acid modifying enzyme produced by *Staphylococcus epidermidis*. J Med Microbiol. 1997; 46(8):693–697. [PubMed: 9511818]

123. von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. Study Group. N Engl J Med. 2001; 344(1):11–16. [PubMed: 11136954]

124. Ji G, Beavis R, Novick RP. Bacterial interference caused by autoinducing peptide variants. Science. 1997; 276(5321):2027–2030. [PubMed: 9197262]

125. Otto M, Echner H, Voelter W, Gotz F. Pheromone cross-inhibition between *Staphylococcus aureus* and *Staphylococcus epidermidis*. Infect Immun. 2001; 69(3):1957–1960. [PubMed: 11179383]

126. Lina G, Boutite F, Tristan A, Bes M, Etienne J, Vandenesch F. Bacterial competition for human nasal cavity colonization: role of Staphylococcal agr alleles. Appl Environ Microbiol. 2003; 69(1):18–23. [PubMed: 12513972]

127. Krismer B, Peschel A. Does *Staphylococcus aureus* nasal colonization involve biofilm formation? Future Microbiol. 2011; 6(5):489–493. doi:10.2217/fmb.11.37. [PubMed: 21585258]

128. Massey RC, Horsburgh MJ, Lina G, Hook M, Recker M. The evolution and maintenance of virulence in *Staphylococcus aureus*: a role for host-to-host transmission? Nat Rev Microbiol. 2006; 4(12):953–958. [PubMed: 17109032]

129. Yao Y, Sturdevant DE, Villaruz A, Xu L, Gao Q, Otto M. Factors characterizing *Staphylococcus epidermidis* invasiveness determined by comparative genomics. Infect Immun. 2005; 73(3): 1856–1860. [PubMed: 15731088]

130. Kozitskaya S, Cho SH, Dietrich K, Marre R, Naber K, Ziebuhr W. The bacterial insertion sequence element IS256 occurs preferentially in nosocomial *Staphylococcus epidermidis* isolates: association with biofilm formation and resistance to aminoglycosides. Infect Immun. 2004; 72(2):1210–1215. [PubMed: 14742578]

131. Gu J, Li H, Li M, Vuong C, Otto M, Wen Y, Gao Q. Bacterial insertion sequence IS256 as a potential molecular marker to discriminate invasive strains from commensal strains of *Staphylococcus epidermidis*. J Hosp Infect. 2005; 61(4):342–348. [PubMed: 16242209]

132. Li M, Wang X, Gao Q, Lu Y. Molecular characterization of *Staphylococcus epidermidis* strains isolated from a teaching hospital in Shanghai, China. J Med Microbiol. 2009; 58(Pt 4):456–461. [PubMed: 19273641]

133. Galdbart JO, Allignet J, Tung HS, Ryden C, El Solh N. Screening for *Staphylococcus epidermidis* markers discriminating between skin-flora strains and those responsible for infections of joint prostheses. J Infect Dis. 2000; 182(1):351–355. [PubMed: 10882623]

134. Ziebuhr W, Krimmer V, Rachid S, Lossner I, Gotz F, Hacker J. A novel mechanism of phase variation of virulence in *Staphylococcus epidermidis*: evidence for control of the polysaccharide intercellular adhesin synthesis by alternating insertion and excision of the insertion sequence element IS256. Mol Microbiol. 1999; 32(2):345–356. [PubMed: 10231490]

135. Rogers KL, Rupp ME, Fey PD. The presence of *icaADBC* is detrimental to the colonization of human skin by *Staphylococcus epidermidis*. Appl Environ Microbiol. 2008; 74(19):6155–6157. [PubMed: 18689520]

136. Miragaia M, Thomas JC, Couto I, Enright MC, de Lencastre H. Inferring a population structure for *Staphylococcus epidermidis* from multilocus sequence typing data. J Bacteriol. 2007; 189(6): 2540–2552. [PubMed: 17220222]

137. Rohde H, Kalitzky M, Kroger N, Scherpe S, Horstkotte MA, Knobloch JK, Zander AR, Mack D. Detection of virulence-associated genes not useful for discriminating between invasive and commensal *Staphylococcus epidermidis* strains from a bone marrow transplant unit. J Clin Microbiol. 2004; 42(12):5614–5619. [PubMed: 15583290]

138. Otto M. *Staphylococcus epidermidis* - the `accidental' pathogen. Nat Rev Microbiol. 2009; 7:555–567. [PubMed: 19609257]

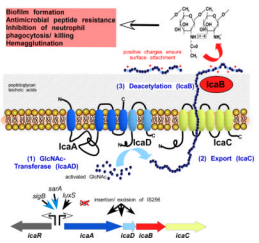

Fig. 1. The exopolysaccharide PIA/PNAG

PIA/PNAG is a partially de-acetylated homopolymer of N-acetylglucosamine residues in β1–6 linkage (top right). It is synthesized by the gene products of the *ica* operon (bottom). Transcription of *ica* is under control of multiple global regulators and other regulatory influences (but not Agr). It also may be inactivated by insertion of IS256. IcaA and IcaD form a glucosaminyltransferase. IcaC likely functions as exporter of the growing PIA chain. IcaB de-acetylates pre-PIA at the cell surface after PIA export. Positive charges introduced by deacetylation are crucial for surface location and the multiple functions of PIA shown at the top left.

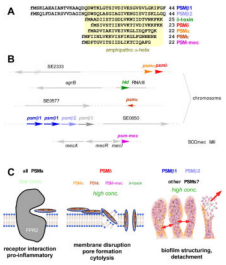

Fig. 2. Phenol-soluble modulins of *S. epidermidis*

A, Amino acid sequences of all *S. epidermidis* PSMs. PSMs are exported as the primary translation products with N-terminal N-formyl-methionine (fM). B, Genetic location of *psm* genes in the chromosome or in the case of *psm-mec*, on SCCmec elements. Gene numbers are according to the genome of ATCC12228. C, Roles of PSMs in inflammation, cytolysis, and biofilm development. All PSMs trigger inflammatory responses by interaction with the FPR2 receptor. PSMδ and to some extent, some other PSMs, function as cytolysins. PSMβ peptides and possibly other PSMs contribute to biofilm structuring and detachment.

Tab. 1

Virulence factors of *S. epidermidis*

Virulence factor	Gene	Function
Biofilm formation		
Primary attachment		
AtlE	*atlE*	Bifunctional autolysin/adhesin
Aae	*aae*	Bifunctional autolysin/adhesin
Teichoic acids	(multiple biosynthetic genes)	Attachment (shown in *S. aureus*)
SdrF	*sdrF*	Binds to collagen
SdrG (Fbe)	*sdrG*	Binds to fibrinogen
SdrH	*sdrH*	Putative binding function only
Ebp	*ebp*	Binds to elastin
Embp	*embp*	Binds to fibronectin
AtlE/Aae	*atlE/aae*	Bind to multiple matrix proteins
Aap	*aap*	Binds to corneocytes
Intercellular aggregation		
PNAG/PIA	*icaADBC*	Intercellular polysaccharide adhesin
Bap	*bap*	Intercellular protein adhesin
Aap	*aap*	Intercellular protein adhesin precursor (requires proteolytic processing for activity)
Embp	*embp*	Intercellular protein adhesin
Teichoic acids		Component of biofilm matrix
Protective exopolymers		
PNAG/PIA	*icaADBC*	Protects from IgG, AMPs, phagocytosis, complement
PGA	*capABCD*	Protects from AMPs, phagocytosis
Resistance to AMPs		
SepA protease	*sepA*	AMP degradation
Dlt, MprF, VraFG	*dltABCD* *mprF* *vraFG*	In analogy to *S. aureus*: D-alanylation of teichoic acids (Dlt), lysylation of phospholipids (MprF), putative AMP export (VraFG)
Aps system	*apsR (graR), apsS (graS), apsX*	AMP sensor, regulator of AMP resistance mechanisms
Toxins		
Enterotoxins		
SEC3, SE1L	*sec3, selL*	Pathogenicity island-located enterotoxins
Phenol-soluble modulins (PSMs)		
PSMα	*psm* α	Cytolysin (moderate activity), pro-inflammatory
PSMβ1, PSMβ2	*psmβ1, psmβ2*	Biofilm-structuring surfactants, pro-inflammatory
PSMδ	*psm* δ	Cytolysin (strong activity), pro-inflammatory
PSMε	*psm* ε	Cytolysin (moderate activity), pro-inflammatory
δ-toxin	*hld*	Cytolysin (moderate activity), pro-inflammatory
PSM-mec	*psm-mec*	Cytolysin (moderate activity), pro-inflammatory
Exoenzymes		
Proteases		
Cysteine protease (SspB, Ecp)	*sspB*	Unknown, tissue damage?

Virulence factor	Gene	Function
Metalloprotease/elastase (SepA)	*sepA*	Tissue damage?, AMP resistance
Glutamylendopeptidase (GluSE, SspA, Esp)	*sspA*	Degradation of fibrinogen and complement factor C5, competition with *S. aureus* (by proteolysis of biofilm matrix proteins?)
Lipases GehC, GehD	*gehC, gehD*	unknown
Others		
Fatty acid modifying enzyme unidentified (FAME)		Detoxification of bactericidal fatty acids