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Review

Staphylococcus epidermidis infections

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Abstract

The opportunistic human pathogen *Staphylococcus epidermidis* has become the most important cause of nosocomial infections in recent years. Its pathogenicity is mainly due to the ability to form biofilms on indwelling medical devices. In a biofilm, *S. epidermidis* is protected against attacks from the immune system and against antibiotic treatment, making *S. epidermidis* infections difficult to eradicate.

Keywords: *Staphylococcus epidermidis*; Cross-infection; Biofilms

1. Introduction

Staphylococcus epidermidis is the most frequently isolated member of the group of coagulase-negative staphylococci. This group is diagnostically distinguished from *Staphylococcus aureus* by its inability to produce coagulase. Together with more rarely found coagulase-negative staphylococci, *S. epidermidis* colonizes the skin and mucous membranes of the human body and represents the major part of the normal bacterial flora of this habitat.

S. epidermidis has gained substantial interest in recent years because it has become the most important cause of nosocomial infections. Whereas *S. epidermidis* has been regarded for a long time as relatively innocuous, it has now generally been accepted as a pathogen. However, *S. epidermidis* requires a predisposed host in order to change from a normal inhabitant of the human skin to an infectious agent, and therefore clearly has to be described as opportunistic. This article deals with the pathogenicity of *S. epidermidis* and the molecular basis of *S. epidermidis* infections.

2. Types of infections

Nosocomial infections represent by far the most frequent type of infections caused by *S. epidermidis*. The 1998 National Nosocomial Surveillance System Report (Hospital Infections Program, National Center for Infectious Diseases, Center for Disease Control and Prevention, Public Health Service, US Department of Health and Human Services, Atlanta, GA, 1998) lists *S. epidermidis* as one of the most often isolated bacterial pathogens in hospitals in general and as the most important pathogen involved in nosocomial bloodstream infections, cardiovascular infections, and infections of the eye, ear, nose, and throat.

In contrast to *S. aureus*, *S. epidermidis* does not usually cause pyogenic infections in non-compromised patients, with the only exception being native valve endocarditis [1]. This is due to its distinctly reduced arsenal of toxins compared to *S. aureus*. In fact, there is only one toxin, the hemolytic peptide δ-toxin, which has been suggested to be involved in necrotizing enterocolitis in neonates [2]. Because of the lack of severely tissue-damaging toxins, *S. epidermidis* infections are usually subacute or chronic.

S. epidermidis very often becomes the major infective agent in compromised patients, such as drug abusers and immuno-compromised patients (patients under immunosuppressive therapy, AIDS patients, and premature newborns). The port of entry into the human body in all of these infections is usually an intravascular catheter [3,4].

The most important group of infections caused by *S. epidermidis* are infections on foreign bodies, such as indwelling catheters and any implanted devices. *S. epidermidis* infections on these devices are complicated by the formation of biofilms, which will be discussed in detail below. Biofilms are often the cause for the difficulty to eradicate *S. epidermidis* infections on an indwelling device,

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due to an impaired penetration of antibiotics to the target and a decreased immune response. Often, removal and reinsertion of the device becomes necessary [5]. The lack of the bactericidal activity of many drugs against staphylococcal biofilms is poorly understood.

3. Virulence factors

S. epidermidis does not produce many toxins and tissue-damaging exoenzymes, as does *S. aureus*. There are a very small number of them, and their role as specific virulence factors has yet to be determined in detail. Generally, the success of *S. epidermidis* as a pathogen has to be attributed to its ability to adhere to surfaces and to remain there, under the cover of a protecting extracellular material, in relative silence.

3.1. Biofilm formation

In *S. epidermidis* infections on indwelling devices, biofilm formation is considered to be the main virulence factor [6]. The extracellular substance surrounding the multilayered cell clusters, often referred to as 'slime' in the past, is composed of bacterial and host products of different chemical composition. In recent years, the components have in part been identified, and biochemical and genetic investigations have produced a much more defined idea of what a staphylococcal biofilm consists of and how it is produced (Fig. 1).

In the course of a foreign body-related infection, two different stages have been distinguished: (1) the primary attachment of the bacteria to the material and (2) the formation of multi-layered cell clusters with cell-cell adherence depending on the production of a "slimy"extracellular substance [7].

3.1.1. Primary attachment

The first stage of staphylococcal colonization of the polymer material of foreign bodies may either proceed as (1) direct attachment of the bacteria to the plastic surface or (2) binding to host-derived matrix proteins which have previously coated the polymer material.

3.1.1.1

Primary attachment to uncoated plastic material

The attachment of *S. epidermidis* to uncoated plastic material is dependent on the physico-chemical properties of the plastic and the bacterial surface. As the plastic surface is hydrophobic, and the primary adhesion of *S. epidermidis* has been shown to be similar on many investigated biomaterials [8], the main parameter determining bacterial adhesion is the hydrophobicity of the bacterial surface [9]. In fact, detergent-like substances of artificial and bacterial origin interfering with the hydrophobic interaction have been shown to lower the degree of adhesion [10].

Although the surface hydrophobicity of bacteria has been thought to be caused by too many factors to be able to find specific molecules responsible for the primary attachment of the bacteria to the plastic material, different approaches have revealed specific bacterial molecules responsible for this kind of interaction.

During a screening of a transposon mutant bank of *S. epidermidis* strain O47 for initial attachment to polystyrene, a mutant had been found that was impaired in attachment and in which the transposon had inserted in the gene for the *S. epidermidis* major autolysin AtlE [11]. The mutant did not produce AtlE and its surface hydrophobicity was reduced, which represents the likely cause for the impaired attachment. AtlE and its degradation products make up the main fraction of *S. epidermidis* surface proteins that are non-covalently attached. Therefore, it is not clear if AtlE represents a protein with specific ability to interact with hydrophobic surfaces or if the difference in mutant and wild-type strain is just due to the fact that most surface proteins are removed in the mutant.

In the meantime, further autolysins have been found to be responsible for the attachment to plastic surfaces and to eukaryotic cells, such as *S. saprophyticus* Aas [12], *S. caprae* AtlC [13] and *Listeria monocytogenes* Ami [14]. In Ami of *L. monocytogenes*, repetitive sequences containing GW motifs seem to be important for the adhesive function [14]. These sequences are also present in the other mentioned autolysins. It therefore appears as if the interaction of autolysins with surfaces is widespread and due to specific parts of the autolysin molecule.

It should also be noted that the AtlE repetitive domains show vitronectin-binding ability and therefore might also be involved in the binding to host-matrix proteins [15].

Recently, primary attachment could also be linked to the surface charge properties of *S. aureus* teichoic acids. A mutant devoid of the ability to D-alanylate teichoic acids, therefore showing an altered charge of the teichoic acids and the bacterial surface in general, revealed decreased attachment to polystyrene [16]. A possible mechanism could be the decreased binding of autolysins to the mutant teichoic acids. Interestingly, a different lipoteichoic acid (LTA)-like molecule, similar to LTA but with a shorter chain length, named lipid S, has recently been found in *S. epidermidis* [17]. Its involvement in biofilm formation has not been investigated yet.

S. aureus also forms biofilms and the factors involved in biofilm formation are very similar in the two species. It is therefore likely that many findings related to biofilm formation, mostly achieved in *S. epidermidis*, but recently—as in this case—also in *S. aureus*, may be transferred from one of these species to the other.

Although the investigation about direct primary attachment to uncoated plastic material has been in the focus of *S. epidermidis* investigators, it is not clear whether this mechanism has a high significance for in vivo biofilm formation on indwelling devices, as it is known that plastic material very rapidly becomes coated by host matrix pro

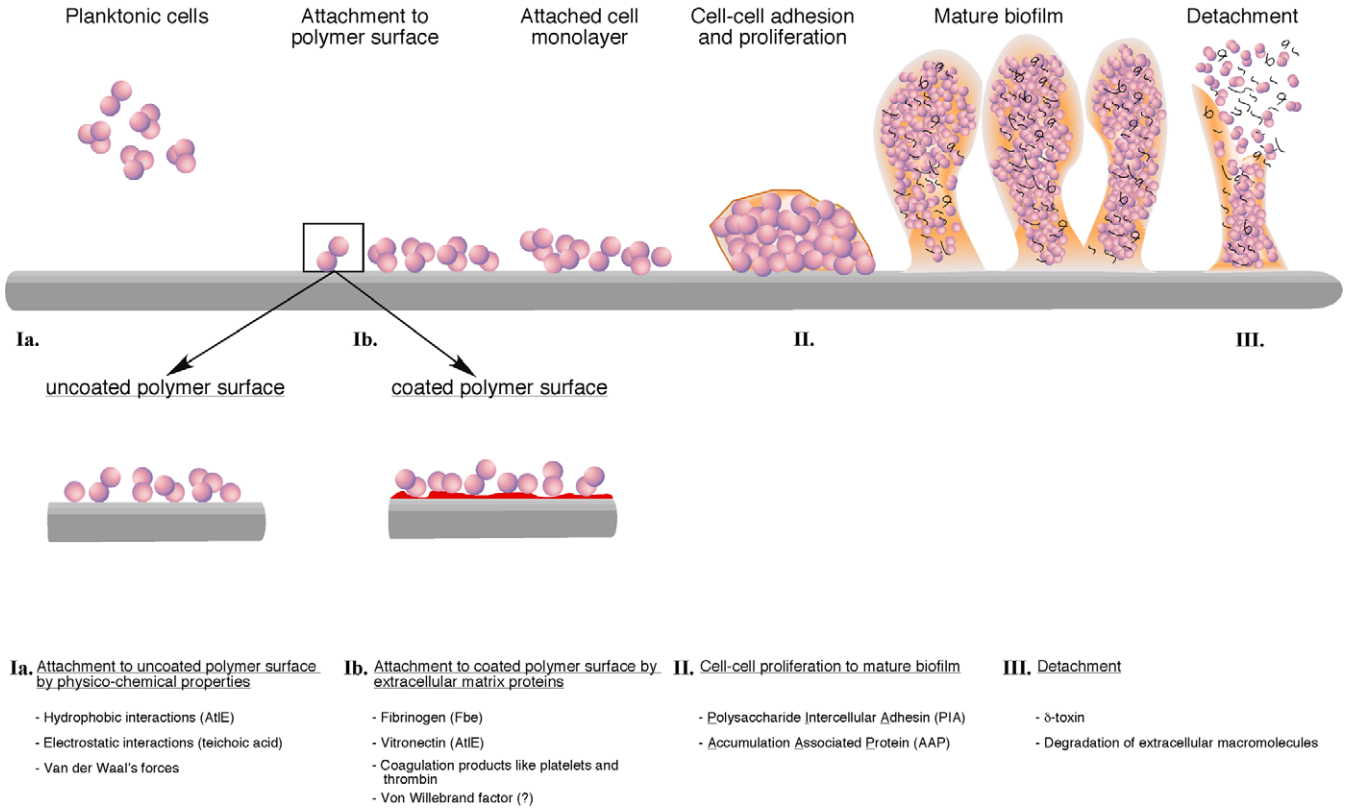

Fig. 1. Model of *S. epidermidis* biofilm formation and involved factors. Fbe, fibrinogen binding protein; AtlE, *S. epidermidis* autolysin.

teins [18]. Preliminary findings using a central venous catheter-associated infection model point towards an in vivo role of autolysin-mediated primary attachment. These findings revealed 50% of rats challenged with the *atlE*-negative transposon mutant developed an infection compared to 80% challenged with the wild-type strain [19]. Further investigations using different animal models will be necessary to confirm the importance of AtlE for an infection in vivo.

3.1.1.2

Primary attachment to plastic material coated with host-derived proteins

As described above, the interaction with host-matrix proteins might represent a more important mechanism of adherence than the direct attachment to plastic. Interestingly, only one MSCRAMM (microbial surface components recognizing adhesive matrix molecules) protein has been found and characterized in *S. epidermidis*: the 119-kDa fibrinogen-binding protein Fbe [20], which shows similarity to the *S. aureus* fibrinogen receptor, or clumping factor (ClfA). The protein harbors an LPXTG domain needed for the covalent linking to peptidoglycan. Surface proteins in staphylococci, as in many other Gram-positive bacteria, are generally linked to the surface via this mechanism by an enzyme called sortase [21]. Very recently, an almost complete genome sequence of *S. epidermidis* strain RP62A has become available. The *S. epidermidis* genome only harbors four genes coding for proteins with LPXTG motifs, the characterized Fbe, a protein harboring a domain with repetitive SD sequences (SdrG), and two further proteins which have also been proposed to be responsible for surface attachment (Aas1 and Aas2). Some but not all strains harbor a fifth surface protein, SdrF [22]. There are also a limited number of non-covalently attached surface proteins, such as SdrH [22]. It remains to be elucidated how such a reduced repertoire of surface proteins, compared to *S. aureus*, renders *S. epidermidis* such a successful surface-colonizing bacteria in the human body.

Clearly, an important question for the future of *S. epidermidis* research will be to rank the contribution of (1) direct attachment of *S. epidermidis* to plastic, and (2) attachment to the surface of an implanted device via host-matrix proteins. Furthermore, it must be investigated if AtlE mediates attachment to eukaryotic cells as does Ami in *L. monocytogenes* and if this mechanism might represent another, maybe more important role of AtlE in vivo.

3.1.2. Intercellular adhesion

The formation of multicellular cell clusters on top of the monolayer of cells attached to plastic or host cells constitutes the second stage of biofilm formation by *S. epidermidis*. Clearly, the mechanisms underlying the adhesion between staphylococcal cells must be different from those enabling the bacteria to adhere to a hydrophobic surface or to specific receptors on host cells.

Several molecules have been proposed to be responsible for this cell-cell adhesion, mostly polymeric carbohydrates and proteins.

A 140-kDa protein named AAP (accumulation-associated protein) has been shown to be responsible for accumulative growth on polymer surfaces [23]. The function of this protein is not clear.

Most genetic and biochemical evidence has been achieved for the involvement of an extracellular polysaccharide in intercellular adhesion, named PIA (polysaccharide intercellular adhesin). PIA is composed of a major polysaccharide I and a minor polysaccharide II. Polysaccharide I is a linear β-1,6-linked 2-deoxy-2-amino-D-glucopyranosyl homopolymer of a chain length of at least 130 residues, which shows *N*-acetylation at about 80-85% of the monomers. Polysaccharide II is very similar in structure, but harbors a limited amount of phosphate and ester-linked succinate [24].

A further polysaccharide, PNSG (poly-*N*-succinyl-glucosamine), has been described to be responsible for intercellular adhesion. It consists of the same backbone structure as PIA, but contains mostly amide-linked succinyl (70-90%) instead of acetyl residues (10-30%). PIA and PNSG seem to be very similar and might even represent the same molecule, a polymer of β-1,6-linked glucosamine residues, partially *N*-acetylated and partially *N*-succinylated [25]. The different chemical analyses are probably due to different purification procedures and/or insufficient release of amide-linked succinate. The different conditions needed for the detection of succinate may have led to the possibly erroneous finding of ester-linked succinyl residues in the first report about PIA polysaccharide II.

A further hint that PIA and PNSG do not represent two different molecules comes from the fact that both polymers are produced by the products of the same genetic locus, *ica* [26,27]. The *ica* locus is composed of the genes *icaA*, *icaD*, *icaB*, and *icaC*. IcaA is an *N*-acetylglucosaminyltransferase, which only reaches low activity without the presence of IcaD. IcaA and IcaD only produce *N*-acetyl oligomers of up to 20 residues of length. IcaC is responsible for the production of PIA of full length, able to react with anti-PIA antisera. The function of IcaB remains unclear [28].

Biochemical investigations have only been performed with *N*-acetylglucosamine as substrate [28]. As PNSG is also produced by the *ica* gene products, it seems obvious that IcaA either also has *N*-succinylglucosaminyltransferase activity, or that an exchange of *N*-acetyl with *N*-succinyl moieties occurs later. No biochemical evidence for the production of PNSG has been achieved so far.

In addition to functioning as an intercellular adhesin, PIA is also responsible for the hemagglutinating activity of *S. epidermidis* [29].

The importance of *ica* as a virulence factor has been shown by a mouse model of foreign body infection [19], and epidemiological evidence has also demonstrated that there is a clear correlation between pathogenicity and the presence of the *ica* genes in virulent *S. epidermidis* strains [30]. None of the saprophytic strains investigated in a recent study harbored the *ica* genes. They were only found in 49% of *S. epidermidis* strains and 61% of *S. aureus* strains from catheters [31]. Furthermore, *ica* was the only determinant discriminating between isolates from the skin and from catheter infections [30].

3.2. Extracellular enzymes and toxins

In contrast to *S. aureus*, *S. epidermidis* produces a very limited number of tissue-damaging exoenzymes and toxins. An extracellular metalloprotease of 32 kDa and a cysteine protease activity have been described in *S. epidermidis* [32,33]. Both proteins show elastase activity. The cysteine protease has been demonstrated to degrade several host matrix proteins and components of the immune system in vitro. However, the contribution of these proteases to the pathogenicity of *S. epidermidis* is highly speculative until now and deserves further investigation. Two very similar lipases are found in *S. epidermidis*, which might be important for skin colonization [34]. Fatty acid modifying enzyme (FAME) works by esterifying fatty acids to cholesterol, thereby destroying their bactericidal properties [35].

The only toxin made by *S. epidermidis* is the mostly *N*-formylated alpha-helical peptide δ-toxin [36]. It is encoded by the *hld* gene located in the regulatory *agr* locus [37]. The δ-toxin causes the lysis of erythrocytes by forming pores in the cytoplasmic membrane [38]. However, the biological function of δ-toxin might be better described as a detergent and it might play a role in the construction of a structured biofilm and in the detachment from surfaces. Purified δ-toxin has been shown to prevent attachment of certain *S. aureus* strains to polymer surface [39]. The biological role of δ-toxin in biofilm formation deserves specific further investigation.

The δ-toxin also forms part of an inflammatory polypeptide complex, which has been named phenol-soluble modulin, as it modulates cytokine and nuclear factor κB production in cells of macrophage lineage [40]. The two other polypeptides of the complex are a 22-aa δ-toxin-like peptide and a 44-aa peptide with similarity to gonococcal growth inhibitor-like peptides from *Staphylococcus haemolyticus* and the SLUSH peptides from *Staphylococcus lugdunensis* (Fig. 2).

3.3. Interference with the host's immune system

Components of the anti-staphylococcal host-defense system include the oxygen-dependent activities of the respiratory burst inside of polymorphonuclear leukocytes (PMNs) and oxygen-independent systems, such as phospholipase A2, platelet microbicidal proteins, and defensins. Defensins are small cationic peptides, and α- and β-defensins can be distinguished according to the spacing of disulfide bridges. They can be found in PMNs, some types of macrophages, and in mucosal secretions. Whereas α-defensins are usually of myeloid origin, β-defensins occur mostly in epithelial

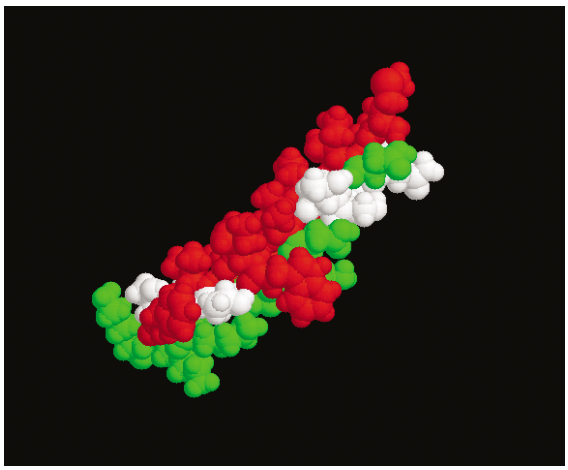

Fig. 2. Staphylococcal δ-toxin (NMR data obtained for *S. aureus* δ-toxin; Protein Data Bank ID: 2DTB). Hydrophobic amino acids are shown in red. Charged amino acids are shown in green.

cells [41]. Recently, a novel human β-defensin has been found and characterized, human β-defensin 3, which shows a much more pronounced activity against *S. aureus* than the other two described human β-defensins 1 and 2 [42].

Staphylococcal factors responsible for the activation of the acute inflammatory host response are most likely fragments of peptidoglycan and teichoic acids. In addition, the phenol-soluble complex discussed above might also contribute to the induction of septic shock.

Most of the studies on the interaction of staphylococci with the immune system have been performed using *S. aureus*. In cases when *S. epidermidis* was included in the study, no generally differing results were achieved. *S. epidermidis* was found to cause less production of macrophage inflammatory protein 1α and IL-8 in human neutrophils compared to *S. aureus*, and might therefore cause a less dramatic inflammatory response than *S. aureus* [43]. However, a more detailed investigation of the immune defense against *S. epidermidis*, especially of the mechanisms found in epithelia, is needed for example to provide a clue to the question why *S. epidermidis* is a more successful colonizer of human skin than *S. aureus* and if this difference might be due to a different interaction of the two species with the host's immune system.

Still, up to now, investigations of this kind have not been performed and many experiments dedicated especially to *S. epidermidis* date from several years ago and focused mainly on the effects of the—at this time still not yet further characterized—'slime substance' of the *S. epidermidis* surface. This substance is thought to play a similar role as the capsule of *S. aureus*: it decreases the phagocytotic activity in murine peritoneal macrophages [44]. Still, the slime substance has also been demonstrated to increase the chemotactic response in human PMNs [45] and to activate the respiratory burst [46]. It remains to be shown which specific components of the 'slime' are responsible for these effects. A recent study demonstrated that the inflammatory response generated by *S. epidermidis* on implanted material is favorable to the persistence of *S. epidermidis*, an effect caused by the intracellular persistence of *S. epidermidis* in pericatheter macrophages [47].

Antibodies to staphylococcal cell walls are usually present in plasma, which explains the high level of "native" resistance against staphylococcal infections and the fact that a staphylococcal infection only occurs in a predisposed host [48].

3.4. Intracellular persistence

S. aureus has been known for several years to be able to persist intracellularly. This mechanism is thought to be responsible for recurring *S. aureus* infections [49]. The bacteria persist in a status of reduced metabolism and reduced production of extracellular virulence factors [50].

As mentioned above, it could also recently be demonstrated that *S. epidermidis* may persist inside pericatheter macrophages, a finding which is very important for our understanding of catheter-related *S. epidermidis* infections [47].

4. Regulation of virulence factors

In *S. aureus*, most extracellular and surface-attached virulence factors are regulated by the *agr* (accessory gene regulator) locus [51]. *agr* is a quorum-sensing system and therefore, the expression of *agr*-regulated targets is cell density-dependent. Generally, when cell density and *agr* activity are low, surface proteins are expressed to allow for tissue colonization. With increasing cell density, *agr* becomes active, the production of surface protein stops, and extracellular degradative exoenzymes and toxins are produced [52].

Further regulatory loci, such as the *sar* locus and the secondary sigma factor *sigB*, also influence the expression of virulence factors, and the regulatory loci have also been shown to influence each other [53–55]. Interestingly, analysis of the *S. aureus* genome, which has recently become available, reveals the presence of many *sar* homologues. It has to be expected that a complicated network of regulatory loci govern the expression of virulence factors in *S. aureus* [56]. *sar* homologues can also be found in the *S. epidermidis* genome. Extracellular conditions, such as glucose or salt concentration, pH, and oxygen pressure, also influence the activity of the regulatory loci mentioned [57]. It is not clear yet which sensors are responsible for this regulation and how the link between extracellular conditions and the activity of *sigB*, *sar*, and *agr* functions on a molecular level.

Although *agr*, *sar*, and *sigB* have all meanwhile been found in *S. epidermidis* [37,58,59], it has remained obscure for a long time whether or not these loci fulfill the same tasks as in *S. aureus*, i.e. regulating the expression of virulence factors. This has mainly been doubted because of the drastic reduction of extracellular and surface-attached virulence factors in *S. epidermidis* compared to *S. aureus*.

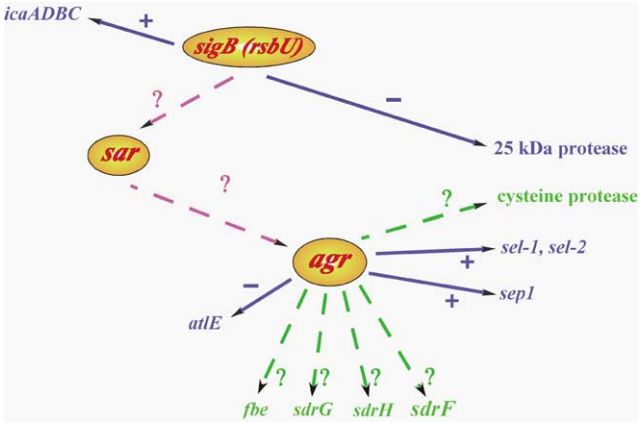

Fig. 3. Model of global regulation of protein expression in *S. epidermidis* involving *agr*, *sar*, and *sigB*. Blue, published proven interactions; green, suggested interactions; purple, supposed interactions in analogy to *S. aureus*. +, positive regulation; –, negative regulation.

The construction of a deletion mutant of the *S. epidermidis agr* system showed a decreased expression of two known extracellular virulence factors, lipase and protease, and a generally increased expression of surface-located proteins [60]. Thus, *agr* has the same task in *S. epidermidis* as in *S. aureus*, the regulation of virulence factors. Still, the finding that *agr* is present also in non-pathogenic staphylococcal species points towards a general role of *agr* in the response to cell-density-dependent changing environmental conditions [61]. In pathogenic species this also includes the change of the production level of virulence factors needed for surface colonization and procurement of nutrients from host tissue, and escape from the deleterious effects of the immune system.

The global regulatory loci of *S. epidermidis* and *S. aureus* also influence biofilm formation. *agr* mutants of *S. aureus* show increased attachment to polystyrene. This is at least in part due to the lack of the detergent-like peptide δ-toxin. About one-fourth of *S. aureus* clinical isolates are naturally occurring *agr* mutants and most of these show an increased ability to attach to polystyrene compared to agr^+ strains [39]. In addition to the fact that this mechanism probably also occurs in *agr* mutants of *S. epidermidis*, *S. epidermidis agr* mutants also show increased production of AtlE, the major autolysin, which mediates primary attachment to hydrophobic surfaces (C. Vuong, C. Gerke, M. Otto, unpublished). In contrast to this, Atl expression is not under the control of *agr* in *S. aureus* [39]. This finding shows that—although many results in biofilm research may be transferable between *S. aureus* and *S. epidermidis*—a separate investigation of the two species is necessary.

The *sigB* locus also influences biofilm formation. A transposon mutant in *rsbU*, a part of the *sigB* regulatory locus, shows decreased production of PIA and decreased biofilm formation [62] (Fig. 3).

5. Bacterial competition

5.1. Bacteriocins

Some *S. epidermidis* strains produce lantibiotics, lanthionine-containing extremely stable antibacterial peptides, such as epidermin, epilancin K7, or Pep5 [63]. It has been discussed that these substances might be important in bacterial competition and that the production of lantibiotics is restricted to *S. epidermidis* among staphylococci. This has been supposed to favor at least some *S. epidermidis* strains in the intra- and inter-species competition [64]. However, while it is possible that lantibiotic production may play a role in bacterial interference, lantibiotic production also occurs in *S. aureus* [65–67]. Even more interesting is the fact that the analysis of the available *S. aureus* genomes reveals the presence of lantibiotic biosynthetic operons on the chromosomes of several strains. Three of six publicly available *S. aureus* genomes harbor a gene cluster for the biosynthesis of a lantibiotic, which appears to be very similar to epidermin of *S. epidermidis* Tü3298 (strains NCTC 8325, Col, and MSSA). Still, the corresponding strains have never been described as producers of antibacterial peptides, and it remains obscure if they are able to produce the corresponding lantibiotic.

5.2. Pheromones

The quorum-sensing system of staphylococci, *agr*, produces a post-translationally modified peptide pheromone [37,68]. It contains a thiolactone and interacts with the *Agr*C histidine kinase on the cell surface [69]. Interestingly, the unusual thiolactone modification is conserved in all staphylococcal species, whereas the primary amino acid sequence of the 7-9 mers varies. Generally, a pheromone activates the *agr* system of self (in its own species), but inhibits the *agr* response of non-self (in other species). This has been first found among *agr* subgroups of *S. aureus*, and this phenomenon also occurs between *S. epidermidis* and *S. aureus*. These pheromones therefore seem to be a means of bacterial competition, by blocking the system in unrelated groups or species, enabling the bacteria to respond appropriately to changing environmental conditions. Because of this activity, *agr* pheromones have also been proposed as anti-staphylococcal therapeutics. Although pheromone derivatives have been made that suppress the *agr* response in all investigated pathogenic species and subgroups [70], a general problem resides in the fact that they always increase the expression of surface proteins, which are important for host tissue colonization. Administration of *S. epidermidis* pheromone to *S. aureus* also increases attachment of *S. aureus* to polystyrene [39]. Therefore, a certain danger exists that *agr*-inhibiting pheromones on the one hand decrease the expression of toxins, but on the other hand may promote colonization and might therefore increase the danger of chronic infection [61].

The *S. epidermidis* pheromone is a very potent inhibitor of *S. aureus agr* subgroups 1 to 3, but not of subgroup 4. Vice versa, only the *S. aureus* subgroup 4 pheromone can inhibit *agr* of *S. epidermidis*, but not the pheromones of the other *S. aureus* subgroups. The *S. aureus* subgroup 4 pheromone differs from that of the most frequently isolated subgroup 1 only by one amino acid, and it seems as if *S. aureus* subgroup 4, which is frequently isolated from skin infections, might have evolved from subgroup 1 by competition with *S. epidermidis* on the skin. Generally, the *S. epidermidis* pheromone seems to be a more potent inhibitor of the *S. aureus agr* system than vice versa. The predominance of *S. epidermidis* on the skin and in chronic infections, for example on indwelling medical devices, might be due to this advantage. As a normal resident of the skin's microflora, *S. epidermidis* might contribute to the body's barrier to colonization by the pathogenic *S. aureus* via quorum sensing cross-inhibition. An interesting exception is *S. aureus* subgroup 4, which seems to have escaped from this unfortunate situation by mutation, probably because of close contact with *S. epidermidis* on the skin [71].

6. Therapy of *S. epidermidis* infections

Treatment of *S. aureus* and *S. epidermidis* infections is generally difficult because of increasing resistance against many antibiotics and because the slime capsule of staphylococci represents an almost impermeable barrier to many antibiotics [72]. For many years, the number of strains with resistance to methicillin, an antibiotic of first choice against staphylococci, has been increasing. Approximately 80% of *S. epidermidis* strains from nosocomial infections are resistant to methicillin, and most are resistant to other antibiotics as well [73]. The resistance patterns of *S. epidermidis* are similar to those of *S. aureus* strains and it can be presumed that resistance occurring in one species can be quickly transferred to the other one. Very recently it has been shown that a *mec* DNA responsible for the resistance towards methicillin was transferred in vivo from one staphylococcal species to the other [74]. Therefore, the problem of antibiotic resistance in staphylococci is never a specific problem of either *S. aureus* or *S. epidermidis*.

Novel antibiotics have been developed to overcome the difficult situation of vancomycin being the last effective antibiotic against many multi-resistant strains and of the appearance of *S. aureus* and *S. epidermidis* strains with intermediate resistance to vancomycin. These antibiotics include for example the oxazolidinone group and quinupristin/dalfopristin [6].

Other methods of controlling infections by *S. epidermidis* include specific hygienic procedures during the insertion of catheters to prevent infection by strains from health care individuals, prophylactic use of systemic antibiotics during surgery, and the covering and incorporating of implanted material by antibiotics and other agents with antibacterial activity.

Targeting specific staphylococcal virulence factors, such as the formation of a slime capsule, is a novel approach for the treatment of staphylococcal infections. Therapeutics preventing the formation of extracellular polysaccharides would drastically increase the bactericidal potential of conventional antibiotics if administered together.

Methods to prevent the formation of slime include the development of anti-PIA antibodies [25], for example, but a more in-depth investigation of the biochemical events during the formation of extracellular macromolecules essential for adhesion, such as PIA but also teichoic acids, might also lead to novel targets for anti-staphylococcal therapy. Targeting surface binding proteins by specific antibodies has also been shown to prevent *S. epidermidis* adhesion to implanted catheters [75]. Furthermore, immunomodulatory substances might be used. Interferon γ has been shown to prevent experimental biomaterial-associated *S. epidermidis* infection [76].

7. Conclusions

The recent advances in genomic research will considerably influence the future investigation of staphylococcal pathogenicity. One complete *S. aureus* genome has already been completed and published [56], several others will be published in the near future. Publication of the *S. epidermidis* genome is expected within 2001. Expression analysis of *S. epidermidis* virulence factors by microarrays will answer questions such as which virulence factors are expressed in different environmental situations, especially in a biofilm setting, and how regulatory systems work and interact.

We are still far from understanding precisely why *S. epidermidis* is such a successful colonizer of human skin and mucous membranes. Investigation of bacterial competition, bacteria-host interaction, and the presence of specific factors enabling *S. epidermidis* to survive in this environment, such as osmo-regulating and -protecting systems, will be needed to answer this important question.

Furthermore, we will have to investigate the processes that make *S. epidermidis* change from an innocuous saprophyte to a pathogen. The evolving field of cellular microbiology, which combines the approaches of researchers in microbiology and cell biology, will certainly be in the focus of *S. epidermidis* research as well.

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