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Staphylococcus epidermidis and its dual lifestyle in skin health and infection

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Abstract

The coagulase-negative bacterium *Staphylococcus epidermidis* is a member of the human skin microbiota. *S. epidermidis* is not merely a passive resident on skin but actively primes the cutaneous immune response, maintains skin homeostasis and prevents opportunistic pathogens from causing disease via colonization resistance. However, it is now appreciated that *S. epidermidis* and its interactions with the host exist on a spectrum of potential pathogenicity derived from its high strain-level heterogeneity. *S. epidermidis* is the most common cause of implant-associated infections and is a canonical opportunistic biofilm former. Additional emerging evidence suggests that some strains of *S. epidermidis* may contribute to the pathogenesis of common skin diseases. Here, we highlight new developments in our understanding of *S. epidermidis* strain diversity, skin colonization dynamics and its multifaceted interactions with the host and other members of the skin microbiota.

The human skin microbiota comprise a complex group of bacteria, viruses, fungi and archaea that mediate dynamic interactions with the host[1]. Considering the surface area of all skin niches, including hair follicles and sebaceous glands, the total area of inhabitable space for microorganisms is more than 30 m^2, making it one of the largest epithelial surfaces for interactions with microorganisms[2]. Bacteria inhabit all layers of the skin from the exterior-facing `stratum corneum` to the interior dermal tissue[3,4]. Early life colonization with microorganisms shapes proper skin development[5–7] and gene expression[8]. The microbiota also exclude pathogens from their skin niche via mechanisms collectively termed colonization resistance[9]. These mechanisms include competition for nutrients, direct inhibition by antimicrobial peptides (AMPs) and/or stimulation of the cutaneous immune response[10]. Taken together, microbial maintenance of skin barrier integrity is vital for homeostasis and disease prevention[10,11].

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The coagulase-negative bacterium *Staphylococcus epidermidis* is a ubiquitous human skin colonizer that is identified at most skin sites through traditional culture methods and metagenomics analyses[1,12,13]. Early phenotypic typing primarily distinguished between pathogenic *Staphylococcus aureus* and other staphylococci by the presence or absence of the coagulase enzyme, respectively[13,14]. Historically, *S. epidermidis* was used as a representative of all coagulase-negative staphylococci (CoNS), yet current evidence suggests that CoNS are far more genetically and functionally distinct from each other than previously appreciated[10,13,15,16]. Many studies regarded *S. epidermidis* as a benign or beneficial member of the skin microbiota that is involved in barrier development, maintenance of homeostasis and control of opportunistic pathogens, yet evidence suggests that *S. epidermidis* leads a far more nuanced lifestyle on skin than previously appreciated[17]. Previous literature also regarded *S. epidermidis* as an 'accidental pathogen', given that many *S. epidermidis* infections are derived from the same strains that inhabit the skin[18–20]. Indeed, *S. epidermidis* remains one of the most frequent causes of implant-associated infections in the United States, and these antibiotic-refractory, biofilm-associated infections are costly for patients and the healthcare system[21]. Further, the global spread of three strains of *S. epidermidis* nearly pan resistant to all classes of antibiotics is also cause for clinical concern[22]. Yet all of these descriptions and assumptions of *S. epidermidis* overly simplify a complex organism. The current question addressed in this Review is how we should appreciate the vast diversity of *S. epidermidis* isolates while reconciling the many benefits of this species with its serious propensity to cause disease.

In this Review, we discuss new developments in our understanding of *S. epidermidis* strain-level diversity, physiology and lifestyle on the skin. We compare positive and negative interactions between the host and *S. epidermidis* during skin colonization or infection. Finally, we discuss the many competitive interactions between *S. epidermidis* and other members of the skin microbiota. Together, a greater appreciation of this complicated organism is imperative for future translational applications, including growing interest in *S. epidermidis* as a candidate for 'bacteriotherapies'[23,24].

Commensal lifestyle

The skin is a harsh environment for microorganisms to colonize[25]. The outermost layer of the epidermis (the stratum corneum) is low in pH and nutrient availability but high in salinity, exposure and concentration of free fatty acids and AMPs[11,25]. By contrast, appendages such as the hair follicle are considerably more anaerobic, shielded from exposure and replete in lipids[25]. Skin can be categorized based on physiology into dry (volar forearm), moist (antecubital crease) or sebaceous or oily (face) sites[1]. Metagenomics analyses of healthy skin demonstrated that the microbial composition of these sites is unique in abundance and species composition[26,27]. The total composition and diversity of the skin microbiome remains stable for up to 2 years, which suggests that microorganisms maintain and reseed themselves in their preferred niche over time in the absence of a substantial disturbance[28]. Healthy human skin is colonized by an array of CoNS species, but *S. epidermidis* is the most abundant CoNS by either traditional culturing methods[12] or metagenomics analyses[27–29] and colonizes all types of skin sites, with a strong propensity

for moist areas[1] (FIG. 1). Additionally, skin sites are colonized by diverse strains of *S. epidermidis* that are genetically distinct within and between healthy humans[27] (BOX 1).

Adhesion and colonization

S. epidermidis must express various adhesins to colonize human skin[30] (FIG. 2). One adhesin implicated in attachment to the stratum corneum is accumulation associated protein (Aap) (FIG. 2a). Aap is a large (140 kDa) rod-like fibril that is `sortase`-anchored to the cell wall and extends away from the cell body[31]. Aap is found in 85–95% of all *S. epidermidis* isolates, which suggests a broadly conserved mechanism for adhesion to `corneocytes`[30,31]. Many *S. aureus* strains express an orthologous giant surface protein, SasG, that also binds human skin components[31]. It was demonstrated in 2021 that Aap-mediated adhesion to corneocytes is dependent on the presence of the amino-terminal L-type lectin domain, although the specific host substrate that binds the lectin remains to be determined[31,32].

S. epidermidis also expresses various other cell wall-anchored proteins important for binding components of the skin matrix (FIG. 2a). One of the largest families of these proteins is the microbial surface components recognizing adhesive matrix molecules (MSCRAMMs), which are characterized by the presence of two adjacent IgG-like folded subdomains and their ability to bind substrates via a 'dock lock and latch' mechanism[30,33]. The *S. epidermidis* MSCRAMM repertoire is substantially smaller than that of *S. aureus*[18]. Members of this family include SdrF, which binds keratin and type I collagen[18,34], and SdrG, which binds fibrinogen[30]. SdrH has also been identified, but its role in binding skin substrates remains to be determined[35]. In addition to the classic MSCRAMMs, other cell wall-associated proteins including the bifunctional autolysin Atl, the giant surface protein Embp and the bifunctional lipase GehD bind vitronectin, surface immobilized fibronectin and collagen, respectively[18,30,36]. Similar to Embp, *S. epidermidis* teichoic acid enhances binding to immobilized fibronectin[37]. Together, this suite of adhesins mediate specific interactions between *S. epidermidis* and the many layers of host skin tissue and the `extracellular matrix`.

Beneficial host interactions

It is now widely appreciated that the skin microbiota, similar to the gut microbiota, can profoundly influence human development and health[7]. In this section, we review how *S. epidermidis* colonization promotes skin barrier development, maintains homeostasis and controls opportunistic pathogens.

Immune priming in skin development and homeostasis.—There is a critical time window in neonatal skin development required for establishing tolerance to commensal microorganisms while maintaining a discrete response to pathogens[5,38]. Regulatory T cells (T_{reg} cells) are important homeostatic mediators at barrier sites, including the gut and skin[39]. In humans, approximately 20% of tissue-resident $CD4^+$ T cells are T_{reg} cells, which is almost twice as many as are found in the colon[39]. Neonatal mice initiated an activated T_{reg} cell-mediated response to commensal microorganism when they were colonized early with *S. epidermidis* that expressed a model T cell antigen[5]. This tolerogenic response was dependent on precise timing of *S. epidermidis* skin colonization and could not be

restored later in life[5,38]. Activated T_{reg} cells localize to the developing hair follicle, a primary site of immune–microbial crosstalk[40] (FIG. 3a). Together with intrinsic hair follicle morphogenesis, *S. epidermidis* application on fetal skin tissue induced the chemokine CCL20 and subsequent T_{reg} cell migration to the follicle[40]. Thus, early *S. epidermidis* skin colonization is one factor in proper development of this cutaneous barrier site. Yet, it is highly likely that many other organisms also contribute to this process given that application of another skin commensal, *Corynebacterium accolens*, similarly induced CCL20 signalling in fetal tissue[40]. Identification of other bacterial species or strains with similar properties will be informative for a global picture of microbial contributions to the development and maintenance of tolerance.

S. epidermidis also promotes cutaneous immune priming through stimulation of mucosal-associated invariant T cells (MAIT cells), which are a predominant unconventional innate-like lymphoid T cell subset in barrier tissues that sense and respond to riboflavin-producing microorganisms[41]. MAIT cell priming depended on early exposure to *S. epidermidis* and other riboflavin-synthesizing bacteria[41]. Primed MAIT cells also mediated tissue repair after punch biopsy injury[41]. However, many skin microorganisms in addition to *S. epidermidis* also synthesize riboflavin and the cumulative contributions of the microbiota to MAIT cell priming remain to be elucidated.

Outside neonatal immune priming, *S. epidermidis* enhances adult skin barrier immunity through a coupled mechanism between dendritic cells and T cells[42]. *S. epidermidis* was detected by non-inflammatory skin-resident $CD11B^+$ dendritic cells, which induced IL-$17A^+CD8^+$ T cell homing to the epidermis and enhanced barrier immunity against the opportunistic pathogen, *Candida albicans*[42]. The ability of *S. epidermidis* to induce $CD8^+$ T cells was restricted to a specific clade (A20) that is enriched on skin from healthy individuals compared with skin from individuals with atopic dermatitis[43]. Finally, the major cell wall component lipoteichoic acid (LTA) of the common laboratory strain *S. epidermidis* O-47 stimulated a distinct ‘IL-10 balanced’ immune signature in dendritic cells via Toll-like receptor 2 (TLR2) signalling, whereas LTA from *S. aureus* did not recapitulate this phenotype[44].

Maintenance of skin barrier integrity is vital for pre-serving homeostasis and preventing allergy or infection. Germ-free mice had altered skin barrier function that could be restored through application of a defined consortium[45]. However, few examples exist of specific microorganisms or microbial gene products that directly control skin barrier function. In 2022, it was revealed that *S. epidermidis* produces a potent `sphingomyelinase` on human skin that increased ceramide content and prevented skin dehydration in vivo[46]. The sphingomyelinase gene was highly conserved across a large cohort of *S. epidermidis* healthy skin isolates, which suggests a species-wide mechanism for skin barrier control[46]. Although this study did not reveal a role for other commensals, other microbial products that facilitate barrier integrity may be identified in follow-up studies.

S. epidermidis and the immune response to barrier injury.—*S. epidermidis* actively coordinates the skin response to injury (FIG. 3a). Commensal staphylococci, including *S. epidermidis*, induced neutrophil CXCL10 signalling in skin wounds that

recruited type I interferon-producing plasmacytoid dendritic cells (pDCs) and drove T cell-independent wound repair[47]. *S. epidermidis*-primed $CD8^+$ T cells have a dual purpose in cutaneous immunity and wound healing[48]. In addition to controlling skin barrier function through interactions with dendritic cells, these cells also maintained a poised type 2 state that could respond to injury and release type 2 cytokines to promote wound repair[48]. However, type 2 immunity is also implicated in the aetiology of various skin disorders[49,50], which suggests that tightly controlled immune–microorganism crosstalk is necessary for optimal skin function and that breakdown of this crosstalk may contribute to immune dysregulation.

S. epidermidis-derived small molecules can have profound impacts on barrier response to insult or injury (FIG. 3a). Healthy skin is dominated by strains of *S. epidermidis* that convert aromatic amino acids into trace amines, and it was shown in 2020 that *S. epidermidis*-derived trace amines accelerated wound healing in a mouse model[51]. The *S. epidermidis*-produced small molecule 6-*N*-hydroxyaminopurine (6-HAP) selectively inhibited proliferation of tumour cell lines but not primary keratinocytes[52]. Exposure to ultraviolet B radiation is associated with chronic inflammation and DNA damage[53], and application of 6-HAP-producing *S. epidermidis* on mouse skin significantly suppressed ultraviolet-induced tumour growth[52]. However, it remains to be determined whether 6-HAP synthesis is conserved in other skin-resident *S. epidermidis* strains, as this phenotype has only been observed in one strain and the genes encoding 6-HAP or its biosynthetic machinery remain elusive. Skin application of butyric acid, a major by-product of *S. epidermidis* glycerol fermentation, also dampened ultraviolet B-induced pro-inflammatory cytokines in vivo[53]. Finally, *S. epidermidis*-derived small molecules can act directly on innate immune sensors. The *S. epidermidis* lipopeptide 78 inhibited TLR3-induced skin inflammation to promote wound healing[54]. Further, LTA from some strains of *S. epidermidis* dampened TNF and IL-6 production after skin injury in a TLR3-dependent manner, which enabled efficient wound healing[55]. The LTA-mediated inhibition of TNF signalling is strain dependent, and LTA from strains isolated from healthy skin (54.3%), healthy conjunctiva (68.8%) and ocular infection (80.4%) inhibited TNF production in keratinocytes in vitro[56]. Additional novel small molecules or metabolic by-products from *S. epidermidis* or other CoNS may also protect skin from internal (that is, tumorous) or external (that is, wounding) injury but remain to be identified.

Colonization resistance.—*S. aureus* is the most common cause of skin and soft tissue infections in the United States and a frequent challenge to skin homeostasis[57]. Methicillin-resistant *S. aureus* (MRSA) is now pandemic and has been classified by the World Health Organization (WHO) as one of 12 pathogens that threaten human health[58]. *S. epidermidis* excludes pathogens, including *S. aureus*, from the skin through various direct and indirect mechanisms (FIG. 3b). *S. epidermidis* strains activated distinct innate immune responses and amplified the keratinocyte antimicrobial response to *S. aureus* infection via secretion of an unidentified factor or factors[59]. In the skin, neutrophil recruitment and netosis enhance *S. aureus* colonization and infection[60]. However, colonization with *S. epidermidis* reduced the number of migrating neutrophils to the site of *S. aureus* infection, although the mechanism of protection remains unclear[60]. An unidentified small molecule (<2 kDa) secreted by *S.*

epidermidis activated the keratinocyte aryl hydrocarbon receptor (AHR) and downstream IL-1α and human β-defensin 3 (hBD3) expression to promote an innate immune defence response[61]. *S. epidermidis*-mediated skin protection is dependent on the integrity of the barrier itself; when mouse skin was tape stripped before challenge with *S. aureus*, the protective effects of *S. epidermidis* colonization were negated[62].

S. epidermidis-derived AMPs also have protective functions on skin (FIG. 3b). The *S. epidermidis* phenol soluble modulins (PSMs) are a family of small, cytolytic amphipathic molecules[18,63]. Both PSMγ (also known as δ-toxin) and PSMδ had cooperative activity with the host AMP LL-37 and enhanced antimicrobial action against *S. aureus* and Group A *Streptococcus* (GAS)[64]. Further, *S. epidermidis* PSMγ was present in the epidermis and dermis of normal human skin and reduced GAS survival in pretreated mouse skin wounds[65]. These studies suggest that *S. epidermidis*-derived antimicrobials could be an additional layer of defence on healthy skin. As only synthetic peptides were used in either study, further investigation of isogenic *S. epidermidis* PSM mutants would be informative. In addition, *S. epidermidis* PSMs are immunomodulatory and share similarities to *S. aureus* PSMs, which can exacerbate skin dysfunction in atopic dermatitis[18,66]. Thus, the regulation of *S. epidermidis* PSMs and the context in which they are made may dictate their positive or negative effects on barrier integrity.

Pathogenic lifestyle

In addition to its role as a commensal, *S. epidermidis* often leads a dual lifestyle as an opportunistic pathogen[17]. Shifts in *S. epidermidis* abundance have been associated with skin diseases, including atopic dermatitis[67], dandruff[68,69], seborrhoeic dermatitis[70,71] and rosacea[72–74]. These observations could suggest an underappreciated potential for *S. epidermidis* pathogenicity in common skin disorders, but the mechanism or mechanisms of interaction remain to be determined. Aside from observations of general dysbiosis, in this section we review specifics of *S. epidermidis* invasive infections, antibiotic resistance and virulence factor production, and the implications of this dual lifestyle for patient health.

Infections

One of the most concerning aspects of *S. epidermidis* physiology is its propensity to cause ‘accidental’ opportunistic infections, where the infectious strain is the same as a colonizing strain[18–20]. *S. epidermidis* is a leading cause of implant-associated infections, prosthetic valve endocarditis and cardiac pacemaker infections[21,75]. Implant infections are serious for the patient, costly for the healthcare system and often only resolved by device removal[21]. *S. epidermidis* is also responsible for 30–40% of nosocomial bloodstream infections, which are often the result of a prior biofilm-associated catheter infection that disseminated into the bloodstream[75]. Bloodstream infections are difficult to treat and can lead to serious complications including sepsis, septic shock and infective endocarditis[21]. *S. epidermidis* bloodstream infections are also a predominant cause of late-onset sepsis in the preterm neonatal population, with long-term complications from infection, including neurodevelopmental impairment and cerebral palsy[76]. Collectively, *S. epidermidis* remains a serious opportunistic pathogen particularly for patients who are immunocompromised.

Clinical prevalence

Although up to 60% of *S. epidermidis* infections are derived from diverse genetic backgrounds[77,78], certain clonal lineages of *S. epidermidis*, particularly sequence type 2 (ST2), are over-represented in infections[22,77,79]. ST2 strains are almost exclusively nosocomial, hospital adapted and drug resistant[22]. Strains of this sequence type are robust biofilm formers and highly invasive[18,80]. Hospital-acquired *S. epidermidis* ST23 (HA-ST23) is now considered a globally important threat to patient health[22]. Strains of HA-ST23 had altered wall teichoic acid (WTA) profiles that augmented pathogenesis in a mouse sepsis model and enabled efficient phage transduction of genetic material between hospital-acquired methicillin-resistant *S. epidermidis* (MRSE) and MRSA, emphasizing the shared potential for virulence between these two organisms[81]. These *S. epidermidis* sequence types represent major pathogens of concern, but more work is needed to understand how they are maintained or spread in the community and why these sequence types, but not others, are associated with infectious disease.

Drug resistance

S. epidermidis strains encode various antibiotic resistance genes often on mobile genetic elements[82]. Staphylococci acquire resistance to methicillin, previously the drug of choice for infections[83], primarily through acquisition of the *mecA* gene[18] encoded on a mobile genomic island referred to as the staphylococcal cassette chromosome *mec* (SCC*mec*)[84]. Methicillin resistance in *S. epidermidis* nosocomial isolates has been reported at 70% or higher, although many studies have not distinguished between *S. epidermidis* and other contaminating CoNS isolates[22,79,85]. Resistance to methicillin is frequently correlated with resistance to other classes of antibiotics, and resistance to all classes of antibiotics has been reported in *S. epidermidis*[22]. In addition to nosocomial infections, MRSE is also frequently isolated from normal skin in adult[86,87] and neonatal[88,89] populations. It has been widely speculated that *S. epidermidis* or other CoNS are the primary reservoir for SCC*mec* acquisition in MRSA and there are now several examples of inter-species transfer of this mobile genetic element, as well as others such as the arginine catabolic mobile element (ACME), between *S. aureus* and *S. epidermidis*[84,87,90–92]. The high levels of shared antibiotic resistance and pathogenicity genes between MRSA and MRSE are a continued threat to patient care and infection outcomes[87].

Virulence factors

The canonical *S. epidermidis* virulence factor arsenal is small compared with *S. aureus* and composed of factors that may have a dual role in commensalism and infection, including proteases, lipases and the PSMs[18]. *S. epidermidis* strains generally do not encode many toxins or exoenzymes, although enterotoxigenic genes were identified in nine strains of *S. epidermidis* in 2019 (REF.[93]). Whole-genome sequencing of more commensal and nosocomial *S. epidermidis* isolates has revealed a larger virulence gene repertoire (that is, genes for biofilm formation, adhesins, haemolysins and exoenzymes) than previously appreciated, which is most likely due to the genetic flexibility of this organism[94] (BOX 1).

Current evidence suggests that the pathogenic or commensal behaviour of *S. epidermidis* often depends on the context[95]. Pathogenic traits are not typically restricted to a single *S.*

epidermidis clonal lineage[96], unlike certain *S. aureus* clonal lineages, which have evolved to be more pathogenic than others[97]. A 2020 metagenomics analysis of healthy skin isolates revealed that *S. epidermidis* virulence genes were variably distributed across subjects and skin sites[95]. Further, the probability of horizontal gene transfer of mobile genetic elements on skin was found to be quite high, with many putative plasmid and phage sequences identified in the genome scaffolds of these healthy skin isolates[95]. Many plasmid scaffolds contained multiple antibiotic resistance genes and the presence of these plasmids was distributed across *S. epidermidis* isolates from multiple body sites, which suggests dynamic horizontal gene transfer among isolates during colonization and represents a potential reservoir of strains with contextually important virulence factors or antibiotic resistance even on healthy skin[95].

The most compelling mechanistic studies of *S. epidermidis* virulence factor production on skin come from 2020 (REF.[98]) and 2021 (REF.[99]) work on the extracellular cysteine protease EcpA. The EcpA protease cleaved integral skin components including desmogelin 1, a key component of `corneodesmosomes`, and the AMP LL-37 (REF.[99]). *EcpA* transcript levels were positively correlated with the abundance of *S. epidermidis* in severe atopic dermatitis lesional sites, tying observational data of *S. epidermidis* abundance in atopic dermatitis to the mechanism of action[99].

EcpA-mediated barrier degradation extends beyond atopic dermatitis lesions, and also has deleterious effects in `Netherton syndrome` lesions[98]. Patients with Netherton syndrome have a single gene mutation in the serine protease inhibitor Kazal type 5 (*SPINK5*) that leads to aberrant epidermal serine protease activity and results in skin barrier disruption and inflammation[98]. Similar to atopic dermatitis, there was a strong positive correlation between the abundance of *S. epidermidis* and the transcription of *ecpA* in lesional Netherton syndrome sites of human volunteers[98]. Further, application of a high EcpA-producing *S. epidermidis* strain on mouse skin recapitulated many of the same phenotypes as application of a staphopain-producing *S. aureus* strain[98]. These data suggest that *S. epidermidis* EcpA is an important virulence factor in atopic dermatitis and Netherton syndrome. However, it remains unclear why all *S. epidermidis* strains retain the *ecpA* gene, but not all strains express EcpA at the same level[99].

Biofilm formation and role in atopic dermatitis

S. epidermidis biofilm formation and regulation have been extensively reviewed, and we refer the reader to the outstanding articles in REFS.[75,100,101]. In brief, many *S. epidermidis* strains mediate biofilm accumulation through the production of polysaccharide intracellular adhesin (PIA; also known as poly-*N*-acetylglucosamine or PNAG), which is encoded in the *icaADBC* operon[102] (FIG. 2b). PIA is composed of repeating β-1,6-linked *N*-acetylglucosamine residues and its production has been linked to protection of the mature biofilm from immune, antibiotic or shear stress[75,103,104]. Production of PIA could also potentially trap water and protect cells from desiccation on the skin, although this is currently only speculation and remains to be investigated[105]. The presence of the *ica* locus has been proposed as a potential determinant of invasive versus commensal *S. epidermidis* isolates with varying success[106,107]. Infection isolates of *S. epidermidis*,

including those isolated from high shear stress environments (that is, catheters), may encode the *icaADBC* locus and produce variable amounts of polysaccharide[103]. However, the same study also found that more than 50% of high shear isolates did not encode the *ica* locus yet could mediate biofilm formation through *ica*-independent mechanisms[103]. Other studies demonstrated that *ica*-positive *S. epidermidis* switches between polysaccharide-dependent and protein-dependent biofilm formation[103]. Strikingly, many *S. epidermidis* isolates from healthy skin do not encode the *icaADBC* locus[108]. Further, *icaADBC* carriage was associated with a fitness defect during human skin colonization and competition with an isogenic *icaADBC* mutant[108].

As an alternative to polysaccharide-based biofilms, *S. epidermidis* also forms proteinaceous biofilms through interactions of surface-associated proteins, including Aap. Initial attachment to surfaces is mediated by the A domain[102,109]. Subsequent biofilm accumulation is dependent on two steps: the metalloproteinase SepA-mediated processing of the A domain to reveal the homodimeric B domain[109,110]; and a ‘zinc zipper’ mechanism, whereby the B-domain G5 repeats homodimerize in a zinc-dependent manner to form a biofilm[111] (FIG. 2b). The orthologous *S. aureus* SasG protein also forms proteinaceous biofilms using a similar zinc-dependent mechanism[112]. Importantly for patient care, *S. epidermidis* and *S. aureus* can form heterogeneous biofilm complexes through SasG and Aap interactions, which suggests a potential role for mixed biofilms during infection, although a role for mixed biofilms on the skin remains unclear[112].

Infection with *S. aureus* is associated with worse disease outcomes for patients with atopic dermatitis; however, some patients experience blooms of *S. epidermidis* rather than *S. aureus*[67,113,114]. Staphylococcal biofilms have been identified in atopic dermatitis eccrine ducts, but not on other body sites unaffected by atopic dermatitis lesions[115]. Further, *S. epidermidis* isolates from lesional atopic dermatitis sites were strong biofilm producers[115]. *S. epidermidis* biofilms in atopic dermatitis lesions may also occlude sweat ducts and exacerbate disease through the induction of itch, although more investigation of the mechanisms of itch induction is warranted[115,116].

In 2021, the biofilm-forming properties of *S. aureus* and *S. epidermidis* were assessed in 400 patients enrolled in the Mechanisms of Progression of Atopic Dermatitis to Asthma in Children (MPAACH) cohort, which is the first US-based longitudinal study of a paediatric population and the potential progression from atopic dermatitis to other atopic diseases[117]. Corneocyte-associated staphylococcal biofilms were identified through scanning electron microscopy analysis of tape-stripped skin in most samples collected[117]. Nineteen per cent of patients were co-colonized with *S. aureus* and *S. epidermidis*, and co-isolated strains of these organisms tended to act cooperatively during in vitro biofilm growth[117]. Although more work is needed to fully describe mechanisms of biofilm cooperativity in atopic dermatitis, the synergistic interactions between *S. aureus* and *S. epidermidis* may be an important mediator of disease outcomes and impair treatment efficacy for patients.

Notably, *S. epidermidis* most likely does not exist only in a biofilm state in atopic dermatitis as the final step in the biofilm life cycle is dispersal[75]. In staphylococci, biofilm dispersal is mediated through upregulation of the accessory gene regulator (*agr*) quorum sensing

system[118,119]. Thus, there is likely to be a balance in the *S. epidermidis* atopic dermatitis life cycle, whereby cells expressing *agr* seed eccrine ducts or other niches, turn down *agr* to form biofilms and then reseed these areas with sequential induction of *agr*. Future work may determine the consequences of these regulatory steps for disease outcomes in atopic dermatitis or other skin conditions.

Microbial competition

S. epidermidis competes with opportunistic pathogens and endogenous members of the normal skin flora for niche dominance. In this section, we review some of these competitive interactions and the implications of these interactions for skin health or disease.

Quorum sensing interference

Among the CoNS, one mechanism of competition is through the *agr* quorum sensing system (BOX 2). This system is conserved across staphylococci[120–122] but best characterized in *S. aureus*, in which it is a master regulator of virulence factors and required for productive skin infection[123,124]. Most studies have focused on direct interactions among CoNS including *S. epidermidis* and *S. aureus* as a means of dampening *S. aureus* virulence factor production and protecting the skin barrier from damage (inter-species competition)[66,125–128]. *S. epidermidis* autoinducing peptide I (AIP-I) was the first identified inter-species inhibitor of *S. aureus agr* quorum sensing, and it has been postulated that this crosstalk could be one mechanism that enables *S. epidermidis* domination on healthy skin while excluding *S. aureus*[125].

However, just as the *agr* system is a master virulence factor regulator in *S. aureus*, it also regulates a smaller but substantial suite of virulence factors in *S. epidermidis*[18]. The extracellular cysteine protease EcpA (discussed above) is directly controlled by *S. epidermidis agr* signalling[129]. Conversely, *agr* also regulates potentially important mediators of skin colonization including the glycerol ester hydrolase (lipase *geh*), PSMs and likely the SepA and Esp proteases[129]. Functional *S. epidermidis agr* signalling was also necessary for colonization of porcine skin ex vivo[129]. Accordingly, *agr* may have a dual purpose for *S. epidermidis* colonization and potential for pathogenicity.

Although fewer *agr*-mediated competitive interactions have been studied between CoNS and *S. epidermidis*, a 2021 study revealed that *Staphylococcus hominis*, another ubiquitous skin commensal, produced an AIP that inhibited the *S. epidermidis agr* quorum sensing system and dampened EcpA production[99]. This type of competitive quorum sensing interaction, or lack thereof, may be insightful in understanding why *S. epidermidis* can bloom and exacerbate atopic dermatitis lesions where the diversity of other CoNS and inhibitory AIP molecules is quite low[67,99].

Antimicrobial peptides and small molecules

Healthy skin is dominated by many CoNS strains that produce antimicrobials (including `bacteriocins`), and loss of antimicrobial-producing strains correlates with development of opportunistic *S. aureus* infections[130]. Although there is evidence that antimicrobial production is a substantial metabolic burden for the producer[131], this conserved mechanism

of bacterial competition is an important component of inter-bacterial warfare on skin[130,132]. Bacteriocins often have a narrow target range, but a few broad-spectrum bacteriocins have been identified in *S. epidermidis* and other CoNS[133–135]. Some skin isolates of *S. epidermidis* produce novel bacteriocins such as epidermicin, which had potent antimicrobial activity against strains of *S. aureus* and vancomycin-resistant enterococci[136]. Other strains of *S. epidermidis* produce lantibiotics (which are bacteriocins that contain a thioether lanthionine ring)[132] such as nukacin IVK45 (REF.[137]) and epilancin 15X (REF.[138]) that may modulate both the skin and nasal microbiome composition, although more work is needed to understand the distribution and relative abundance of these strains on healthy skin.

Other *S. epidermidis* molecular products mediate distinct competitive interactions with *S. aureus*. Some strains of *S. epidermidis* synthesize and export the purine analogue 6-thioguanine, which inhibited *S. aureus* growth, de novo purine biosynthesis and virulence factor production and protected skin from dermonecrotic damage[139] (FIG. 3b). However, far fewer strains of *S. epidermidis* contained the biosynthetic pathway for 6-thioguanine compared with other CoNS, which suggests that this may not be a primary mechanism of pathogen exclusion for *S. epidermidis*[139].

Competition with cutibacterium acnes

There is substantial interest in understanding the interactions between *Cutibacterium acnes* (formerly *Propionibacterium acnes*) and *S. epidermidis* given their coexistence in the hair follicle and inconclusive contributions to the pathophysiology of acne vulgaris[140–142]. *C. acnes* engages in various strain-dependent antagonistic interactions with *S. epidermidis* through the production of antimicrobial compounds[143] (FIG. 4). *C. acnes* strains also produce short-chain fatty acids that inhibited *S. epidermidis* polysaccharide-dependent biofilm formation and sensitized *S. epidermidis* to antibiotic treatment[144]. It was discovered in 2020 that the novel *C. acnes* thiopeptide antibiotic, cutimycin, directly controlled staphylococcal colonization of the hair follicle[145]. The cutimycin locus was present in the *C. acnes* population in the majority of a cohort of healthy volunteers and its presence was stable on a specific individual over time[145]. Sampling of hair follicle content revealed significantly greater abundances of *C. acnes* compared with *S. epidermidis* when the locus for cutimycin was present, which suggests a specific role for *C. acnes* in controlling *S. epidermidis* growth and niche colonization in the hair follicle.

S. epidermidis–C. acnes competition is not unidirectional, and *S. epidermidis* directly competes with *C. acnes* through the fermentation of skin-available glycerol[146]. *S. epidermidis* ferments glycerol to short-chain fatty acids, including acetic acid, butyric acid, lactic acid and succinic acid[146]. However, succinic acid was the most effective inhibitor of *C. acnes* growth in vitro and in vivo[146]. As both *S. epidermidis* and *C. acnes* can ferment glycerol, sucrose has shown promise as a *S. epidermidis*-specific fermentation initiator to boost its antimicrobial production against *C. acnes*[147]. Supporting a potential anti-inflammatory role in acne, *S. epidermidis* LTA dampened *C. acnes*-induced skin inflammation in vivo via TLR2 induction of the keratinocyte small RNA miR-143 (REF.[148]). In another potential mechanism of competition, some strains of *S. epidermidis* encode an ESAT6 secretion system, similar to the type seven secretion systems identified in

Mycobacterium tuberculosis and *S. aureus*[143]. This system might be used to engage in inter-bacterial competition with *C. acnes*, although an isogenic mutant in the *S. epidermidis* ESAT6 system is needed to confirm these genotypic findings. Additionally, it is unclear whether this system is only important for competition with *C. acnes* or whether it could also be used for competition with other organisms[143]. Together, *S. epidermidis* may have a beneficial role in containing *C. acnes* pathogenesis in certain contexts, but skewing conditions to favour *S. epidermidis* outgrowth in the follicle could also have negative consequences for the host given the intrinsic ability of *S. epidermidis* to cause accidental or opportunistic infections.

Competition with *S. aureus* in the nasal cavity

S. aureus is considered a poor or transient healthy skin colonizer and more often asymptomatically colonizes the anterior nares[149–151]. Prior nasal colonization with *S. aureus* is strongly associated with autoinfection of distal skin sites[149,150,152]. However, high nasal colonization with *S. epidermidis* is associated with lower abundance of opportunistic pathogens[153]. Much like skin colonization resistance, *S. epidermidis* actively excludes *S. aureus* from the nasal environment. Some isolates of *S. epidermidis* secrete the extracellular serine protease Esp that degrades *S. aureus* biofilms[154]. Esp cleaved many *S. aureus* cell wall-associated proteins in an established biofilm matrix, including the fibronectin binding protein A (FnbA), the fibrinogen-binding protein Efb and the IgG-binding protein (Spa)[155]. However, *S. aureus* also encodes the homologous V8 serine protease[156]. It remains unclear if or how these strains may respond to Esp-mediated clearance and a role for the V8 protease was not addressed in either Esp study. Some strains of *S. epidermidis* may also compete with *S. aureus* for binding sites on desquamated nasal epithelial cells (that is, squames)[157]. The *S. epidermidis* Aap and *S. aureus* SasG are homologous, cell surface-associated proteins that individually mediate attachment to nasal squames[157]. However, a clear role for competition between these two proteins in the nose remains to be determined. Many *S. epidermidis* strains also induce expression of the AMPs LL-37 and human hBD3 in nasal keratinocytes to kill *S. aureus*[153].

Therapeutic applications

There is growing interest in the usefulness of *S. epidermidis* as a biotherapeutic, whereby its beneficial attributes could be harnessed to treat dysbiotic skin disorders such as atopic dermatitis, psoriasis or others[23,133,141] (TABLE 1). There are several approaches to formulating biotherapeutics, including application of live `probiotics`, supplementation with `prebiotics` to support the growth of select organisms or administration of inanimate microbial products via `postbiotic` therapy[158]. Clinically, it will be imperative to select the correct strain of *S. epidermidis* so that the benefits of its anti-inflammatory or immunomodulatory properties outweigh the risks of its potential to harbour or acquire virulence factors. In a small trial, application of lyophilized *S. epidermidis* on the face of human volunteers significantly boosted facial lipid concentration and moisture retention compared with controls[159]. Probiotic application of an Esp protease-producing strain of *S. epidermidis*[154] could represent a viable alternative to standard mupirocin treatment[160] to clear *S. aureus* from the nares as long as the growth or potential for pathogenicity of the

strain could be managed. One approach for controlling growth of a live biotherapeutic is through nutrient auxotrophy, whereby a specific substrate must be provided in *trans* for an organism to grow. An alanine auxotroph engineered strain of *S. epidermidis* recently showed promise for use as a live biotherapeutic whereby bacterial growth and colonization levels could be modulated without the need for antibiotic marker insertion or antibiotic application[161].

Combinatorial bacteriotherapy is another potential option for patients. A cream mixture of *S. epidermidis* and *S. hominis* with antimicrobial activity significantly reduced the *S. aureus* burden on the skin of five patients with atopic dermatitis after 24 h[130]. Another group found that combinatorial therapy with *S. epidermidis* and a skin commensal strain of *Staphylococcus cohnii* significantly decreased the disease activity index score in germ-free mice that were topically infected with *S. aureus*[162]. In the context of re-establishing a disrupted microbiota (that is, prebiotic therapy), a commensal strain of *Lactobacillus brevis* promoted *S. epidermidis* recolonization and improved barrier function in a group of patients with severe dry skin[163]. However, *L. brevis* is not considered a member of the normal skin flora and the mechanism of this interaction remains unclear. These early studies suggest promising applications for *S. epidermidis* in the treatment of various skin diseases. Nevertheless, there remain significant challenges to implementation of bacteriotherapy. More work is needed to fully appreciate potential *S. epidermidis* pathogenicity, especially possession or acquisition of virulence factors as well as broad-spectrum resistance to methicillin and other antibiotics.

Conclusions and future perspectives

S. epidermidis is a complex skin colonizer that mediates positive and negative interactions with the host. Given the rise of antibiotic-resistant infections and the link between many skin diseases and microbial dysbiosis, there is intense interest in harnessing commensals and their molecular products for bacteriotherapies[23,158] to treat conditions such as acne[141,147], atopic dermatitis[23,164–166] or psoriasis[158]. *S. epidermidis* is easy to isolate[1,12], often stimulates positive immune responses[41,52,59] and produces various novel antimicrobials[65,134,138]. However, *S. epidermidis* retains considerable potential for pathogenicity through strain-level variation[95], genetic flexibility[77,84] and production of an array of virulence factors that have been implicated in worsening the pathologies of atopic dermatitis[99] and Netherton syndrome[98]. Aside from *S. epidermidis*, other members of the CoNS normal community, including *S. hominis*, have also shown great promise as a source of novel antimicrobials[130,133] and for live bacteriotherapy application in atopic dermatitis lesions[24]. It is time to develop novel therapeutics or probiotics, but we must proceed with caution and respect the unintended consequences of reshaping microorganisms such as *S. epidermidis* while expecting them to behave predictably.

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Glossary

Stratum corneum
The topmost layer of the epidermis, composed of dead keratinocytes linked together in a ‘brick and mortar’ structure by extracellular lipids.

Coagulase
A polypeptide secreted by *Staphylococcus aureus* that promotes blood clotting and was historically used to distinguish this organism from less pathogenic coagulase-negative staphylococci (CoNS) for clinical identification.

Sortase
An enzyme that links surface proteins to the gram-positive cell wall.

Corneocytes
Dead keratinocytes that compose the topmost layer of the epidermis.

Extracellular matrix
A structural support system within the dermal skin layer composed of various proteins including collagen and elastin.

Sphingomyelinase
A bacterial esterase, often implicated in virulence, that cleaves sphingomyelin.

Pangenome
The entire set of genes within a species, including conserved, core genes found in every strain and variable genes not conserved in every strain.

KEGG modules
Families of genes that are linked to specific cellular functions.

Phase variation
The reversible, heterogeneous switch in gene expression profiles within a clonal population of bacterial cells.

Plasmacytoid dendritic cells
(pDCs). A specialized subpopulation of dendritic cells involved in immunosurveillance and antigen recognition.

Corneodesmosomes
The major intercellular adhesives within the stratum corneum.

Netherton syndrome
A rare genetic disorder characterized by a mutation in a serine protease inhibitor that leads to severe, often life-threatening, skin abnormalities.

Bacteriocins
Ribosomally synthesized peptides made by many types of bacteria with varying mechanisms of antimicrobial activity.

Kin selection

The theory that genetic relatedness of a population of cells should lead to more cooperativity and increased fitness of that specific population.

Probiotics

Live microorganisms applied to re-regulate a dysbiotic community or actively exclude an opportunistic pathogen.

Prebiotics

Nutrients or other substrates added to alter species composition that favour select microbial growth and exclude opportunistic pathogens.

Postbiotic

Dead or otherwise inanimate bacteria or a bacterial product applied to promote skin barrier function.

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Box 1 |

Staphylococcus epidermidis genetic flexibility

Understanding of *Staphylococcus epidermidis* strain heterogeneity was previously limited by several factors, including the assumption that all *S. epidermidis* strains were genetically similar and, thus, behaved similarly and the focus on understanding host–pathogen relationships at the expense of commensals. Many initial efforts to genetically characterize *S. epidermidis* focused on multilocus sequence typing or pulse field gel electrophoresis to identify traits that could distinguish pathogenic strains from commensal strains[170]. These methods can reveal certain allelic relationships among strains, but they are inherently low resolution and do not provide substantial insight into the total genomic heterogeneity in a population. Recent advances in whole-metagenome shotgun sequencing and in silico modelling enabled higher taxonomic resolution and provided insight into microbial functionality in disparate environments, but a large gap remains in our understanding of intra-species diversity in the microbiome and its implications for skin health[171,172].

A sequencing survey of healthy and nosocomial *S. epidermidis* isolates was the first to substantially improve the number of fully sequenced *S. epidermidis* genomes[80]. It revealed that the *S. epidermidis* genome is composed of approximately 80% core and 20% variable genes[80]. These variable genes indicated that *S. epidermidis* has an open `pangenome`, or high potential to acquire new genetic traits especially through mobile genetic elements (also called the mobilome), including phages and plasmids[80,82]. Indeed, the most enriched functions of the variable genome included replication, recombination and repair, as well as transcriptional regulators and defence mechamisms[80]. It is well established that mobile genetic elements profoundly affect *S. epidermidis* adaptation to various niches and lifestyles, and many mobile genetic elements have been associated with the propensity of certain *S. epidermidis* strains to cause infection[77].

Underlying genetic diversity among strains and exchange of mobile genetic elements among strains or species can influence phenotypic behaviour and adaptation to various niches. *S. epidermidis* functional specialization during skin colonization is apparent in the variety and diversity of strains that colonize distinct ecological niches (dry, moist, sebaceous), especially those that are more isolated from intra-host transmission (toe web)[95]. The first longitudinal (two to four time points over 1 month), multibody site, multi-volunteer metagenomic interrogation of *S. epidermidis* strain-level diversity of healthy adult skin was published in 2020 (REF.[95]). Subjects from this study were colonized by multiple lineages of *S. epidermidis* with distinct genetic content, and the predicted functionality of this genetic content, including `KEGG modules`, lantibiotics and biosynthetic gene clusters, was dependent on the host and the skin site[95]. Further, there was strong evidence of horizontal gene transfer between skin sites, especially for antibiotic resistance and virulence-associated genes[95]. Together, *S. epidermidis* strain-level variation is likely to underlie niche specialization and colonization along with contextual potential for pathogenicity.

Genetic flexibility is also apparent during infection, as isolates of *S. epidermidis* from pacemaker-associated endocarditis were shown to undergo within-host adaptation to become stronger biofilm formers and more antibiotic tolerant[173]. Insertion elements are another driver of phenotypic diversity among *S. epidermidis* strains. The insertion sequence IS256 is essential for genetic plasticity as it mediates `phase variation` in biofilm formation and spontaneous chromosomal deletions, and can also function as a gene promoter[170]. Insertions in the exopolysaccharide-forming locus *icaADBC* and the quorum sensing accessory gene regulator (*agr*) system highlight some of the phenotypic variations driven by IS256 (REF.[170]). It has been reported that the presence of IS256 is associated with pathogenic lineages of *S. epidermidis*, and its presence or absence has been proposed as a 'molecular marker' to differentiate invasive strains from commensals[77,107,174]. However, there is at least one report of commensal *S. epidermidis* isolates that retain the IS256, although the relative prevalence of IS256-positive commensals was much lower than IS256-positive invasive strains[80].

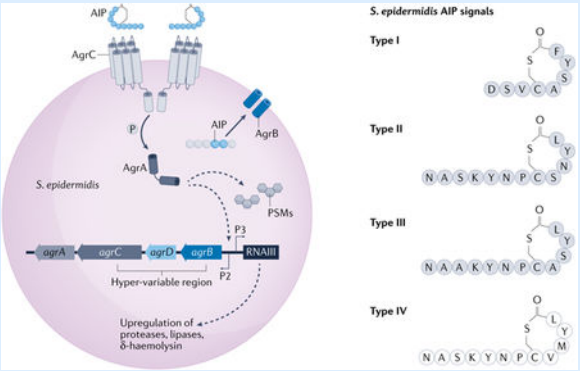
Transfer of mobile genetic elements among staphylococcal species was originally thought to be rare given the presence of 'impenetrable' restriction modification systems[175] and CRISPR loci[176] that degrade foreign DNA. However, more recent evidence suggests that the presence of CRISPR loci in coagulase-negative staphylococci (CoNs) is not as high as previously assumed[177]. additionally, there are multiple examples of inter-species genetic transfer between *S. epidermidis* and *Staphylococcus aureus* including exchange of enterotoxin-encoding genes[93], metal toxicity resistance genes[87] and the staphylococcal cassette chromosome *mec* (SCC*mec*), which encodes methicillin resistance[84]. In the context of patient care and antibiotic treatment, the importance of this genetic flexibility and exchange cannot be overstated. It suggests that genetic adaptations that are advantageous to one species can be transferred to another to promote the persistence of highly adapted, multidrug-resistant pathogenic lineages[87]. Together, the fundamental genetic flexibility of *S. epidermidis* enables it to be a highly adaptable specialist in various contexts from commensalism to invasive infection.

Box 2 |

The *Staphylococcus epidermidis* accessory gene regulator quorum sensing system

The *Staphylococcus epidermidis* accessory gene regulator (*agr*) is a conserved two-component quorum sensing system that senses and responds to changes in bacterial population density[120,178]. Upon reaching sufficient external concentration (a quorum), the signal autoinducing peptide (AIP) binds to the membrane-bound histidine kinase receptor AgrC, which induces receptor dimerization and autophosphorylation followed by subsequent phosphorylation of the response regulator, AgrA[120,122] (see the figure, left panel). AgrA binds between chromosomal promoters P2 and P3 to induce transcription of the *agrBDCA* operon and the major effector transcript RNAIII, which post-transcriptionally regulates a small suite of factors involved in colonization and pathogenesis of the organism[120,122]. AgrA also directly regulates expression of the immunomodulatory, cytolytic phenol soluble modulins (PSMs)[63].

A hyper-variable region spanning *agrBDC* determines the *agr* class, or allelic variant, of every *S. epidermidis* strain (see the figure, right panel). There are four described allelic variants of *S. epidermidis*, and each senses and responds to its own cognate AIP (denoted type I–type IV)[95,129]. The structures of *S. epidermidis* AIP-I, AIP-II and AIP-III (grey) were confirmed by mass spectrometric analysis[129], whereas AIP-IV is the most recently discovered AIP and the structure has not yet been confirmed (white)[95]. Certain *S. epidermidis agr* classes cross-inhibit non-cognate *agr* systems via intra-species crosstalk. AIP-I inhibited *agr*-II and *agr*-III systems (and vice versa), whereas AIP-II and AIP-III do not cross inhibit, which is likely to be due to similarities in their structures[129]. Although a functional role for *S. epidermidis agr* heterogeneity remains to be determined, it is widely speculated that it may enable `kin selection` via intra-species competition and/or functional advantages in one niche over another[95,125].



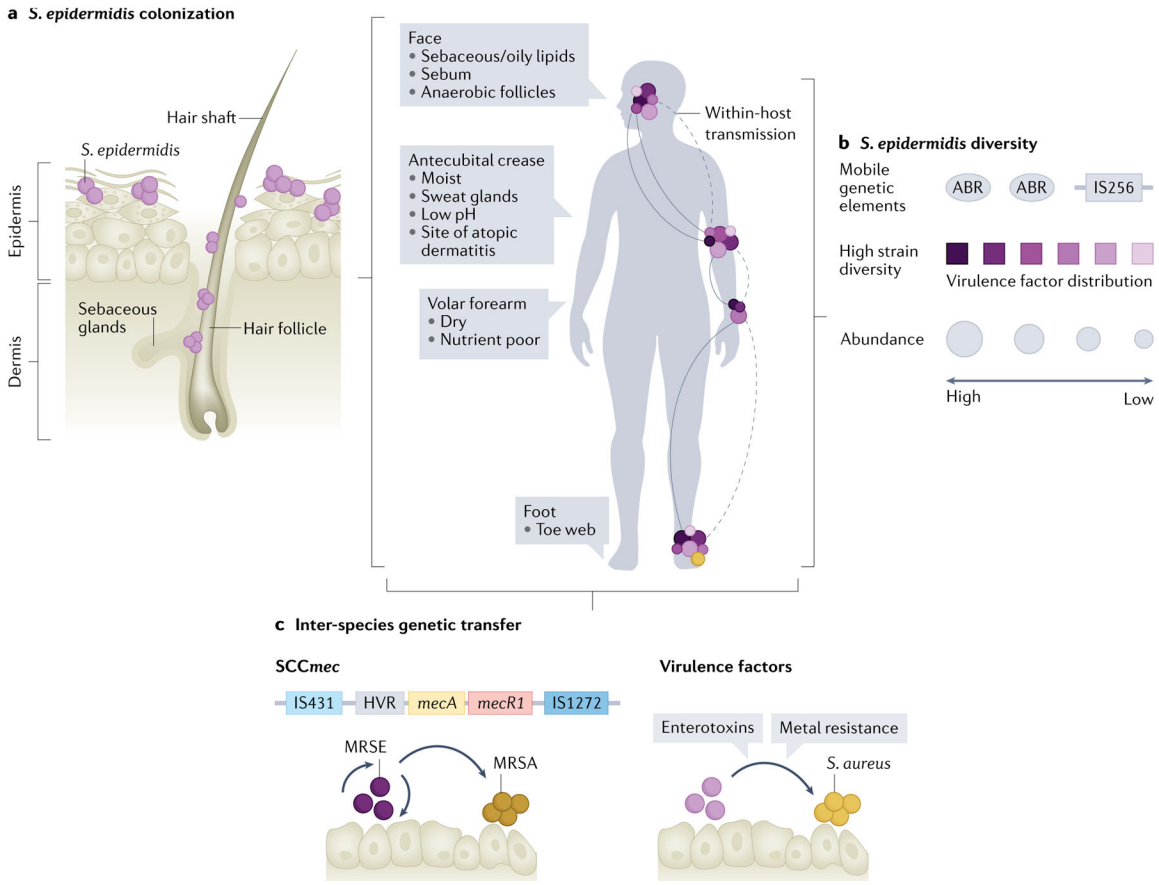


Fig. 1 |. The commensal lifestyle of *Staphylococcus epidermidis*.

a | The skin can be subdivided into different ecological niches based on physio-chemical properties such as density of sebaceous and sweat glands, level of moisture and oxygen tension. *Staphylococcus epidermidis* colonizes all these environments at different densities, including the outermost stratum corneum as well as the interior of the hair follicle, and is a dominant colonizer of moist sites. **b** | Recent metagenomics studies revealed high strain-level heterogeneity of skin-colonizing *S. epidermidis* (represented by various colours) (BOX 1). These strains share genetic content, including virulence factors and antibiotic resistance factors (ABRs), via horizontal gene transfer of mobile genetic elements, including plasmids, phages and transposable elements (such as the insertion sequence IS256). Body sites are colonized by varying levels of *S. epidermidis* (indicated by circle size) with the highest density of *S. epidermidis* in moist or sebaceous sites. **c** | Horizontal gene transfer of the staphylococcal cassette chromosome *mec* (SCC*mec*), which encodes resistance to methicillin, between *S. epidermidis* and *Staphylococcus aureus*. Other virulence factors can also be exchanged between these organisms, including enterotoxins and genes for metal resistance. MRSA, methicillin-resistant *S. aureus*; MRSE, methicillin-resistant *S. epidermidis*.

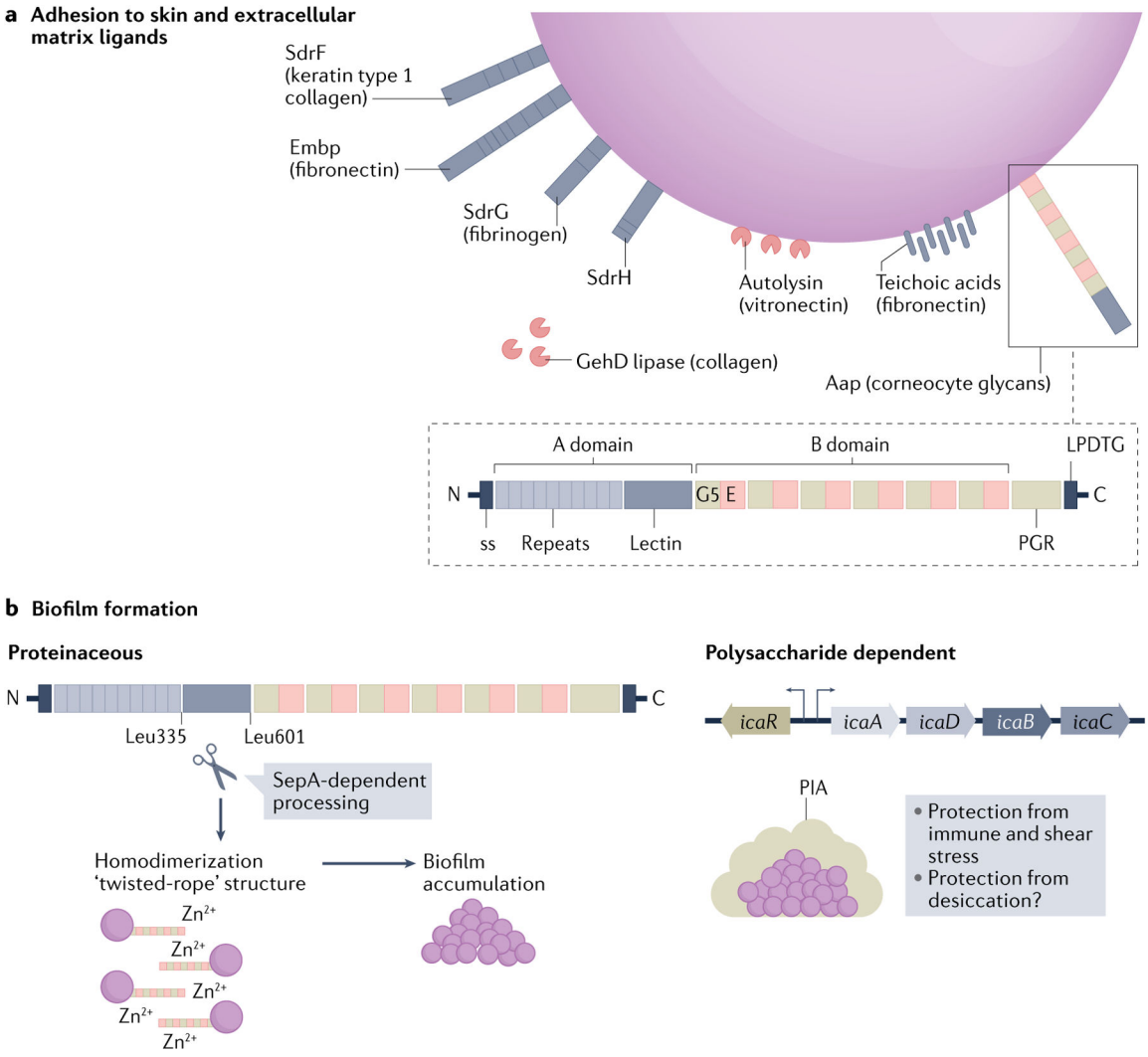


Fig. 2 |. *Staphylococcus epidermidis* adhesion and biofilm formation.

a | *Staphylococcus epidermidis* binds components of skin (ligands indicated, if known) and the extracellular matrix through expression of surface-anchored proteins, called adhesins. This family of microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) includes several serine aspartate repeat containing (Sdr) proteins. Other non-MSCRAMM cell wall-associated proteins with roles in cellular adhesion include the giant Embp protein, the bifunctional autolysin and the bifunctional lipase GehD. Many *S. epidermidis* isolates encode the large (140 kDa), multi-domain accumulation associated protein (Aap) that is anchored to the cell wall by sortase via the LPDTG motif in the carboxy terminus. Aap export from the cell is facilitated by the amino-terminal secretion sequence (ss). The A domain is composed of short, 16 amino acid repeats followed by a lectin-like domain. The B domain contains a variable number (5–17) of 128 amino acid repeats of G5 domains (named for their conserved glycine residues) and E spacer regions. The C-terminal proline–glycine rich region (PGR) and the cell wall anchoring motif (LPDTG) are also indicted. Aap specifically mediates attachment to the host stratum corneum through the A-domain lectin, which leads to epithelial colonization. **b** | Aap also

mediates proteinaceous biofilm attachment and accumulation. The metalloproteinase SepA cleaves the N-terminal A domain of Aap at specific amino acid residues (Leu335 and Leu601). Cleavage is followed by homodimerization of the B domain in a zinc-dependent manner. Many, but not all, *S. epidermidis* strains have the *icaADBC* operon, which encodes polysaccharide intracellular adhesin (PIA; also known as poly-*N*-acetylglucosamine (PNAG)), as well as the *icaR* gene, which encodes a regulatory protein. PIA is composed of repeating β-1,6-linked *N*-acetylglucosamine residues and its production promotes biofilm formation. Such polysaccharide-dependent biofilms may protect mature biofilms from immune, antibiotic or shear stress. In addition, the polysaccharide has been speculated to aid in protection against desiccation but further investigation is warranted[105].

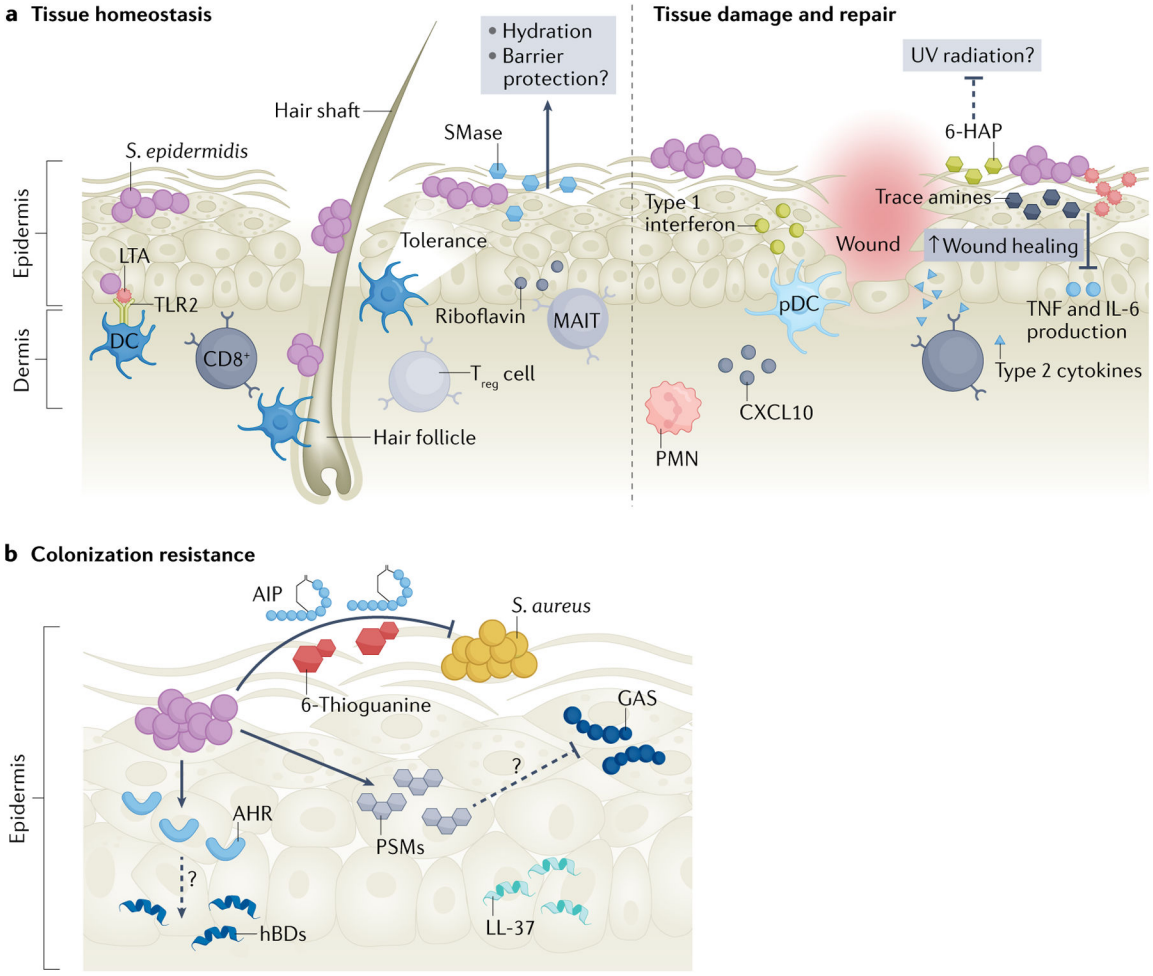


Fig. 3 |. *Staphylococcus epidermidis* mediates skin homeostasis, barrier repair after injury and colonization resistance.

a | Homeostasis: early-life *Staphylococcus epidermidis* skin colonization in the hair follicle primes the cutaneous immune response to tolerate future commensal colonization via activation of regulatory T cells (T_{reg} cells). *S. epidermidis*-derived riboflavin is sensed by unconventional mucosal-associated invariant T cells (MAIT cells), priming them to become a dominant type 17 effector subset. $CD11B^+$ dendritic cells (DCs) sense *S. epidermidis* healthy adult skin colonization and stimulate $CD8^+$ T cell migration. *S. epidermidis* lipoteichoic acid (LTA) is sensed by dendritic cells via Toll-like receptor 2 (TLR2) signalling. *S. epidermidis* produces a potent sphingomyelinase (SMase) on human skin that increases ceramide content, thus promoting skin hydration and, possibly, barrier integrity. Barrier repair: *S. epidermidis* and its molecular products including trace amines, lipopeptide 78 and LTA dampen the inflammatory response (TNF and IL-6 production) to promote wound healing. *S. epidermidis*-recruited polymorphonuclear leukocytes (PMNs) stimulate plasmacytoid dendritic cells (pDCs) via CXCL10 signalling to secret type I interferons in the wound site to aid healing. $CD8^+$ T cells express type 2 cytokines to promote wound repair. 6-*N*-hydroxyaminopurine (6-HAP) may also protect skin from tumour development, although further studies are necessary to clarify the mechanism and the 6-HAP biosynthetic pathway (dashed line). **b** | Colonization resistance: *S. epidermidis* excludes Group A

Streptococcus (GAS) and *Staphylococcus aureus* from skin. Autoinducing peptides (AIPs) block *S. aureus* quorum sensing and the purine analogue 6-thioguanine inhibits *S. aureus* purine biosynthesis. *S. epidermidis* phenol soluble modulins (PSMs) synergize with host antimicrobial peptides (AMPs) including LL-37 to augment killing of *S. aureus* and GAS, although the mechanism warrants further investigation (dashed line). Unidentified secreted factors from *S. epidermidis* signal via TLR2 to stimulate keratinocyte production of human β-defensin 2 (hBD2) and hBD3. Unidentified *S. epidermidis* factors activate the keratinocyte aryl hydrocarbon receptor (AHR) and increase hBD3 expression. Some strains of *S. epidermidis* produce AMPs that specifically kill certain pathogenic species.

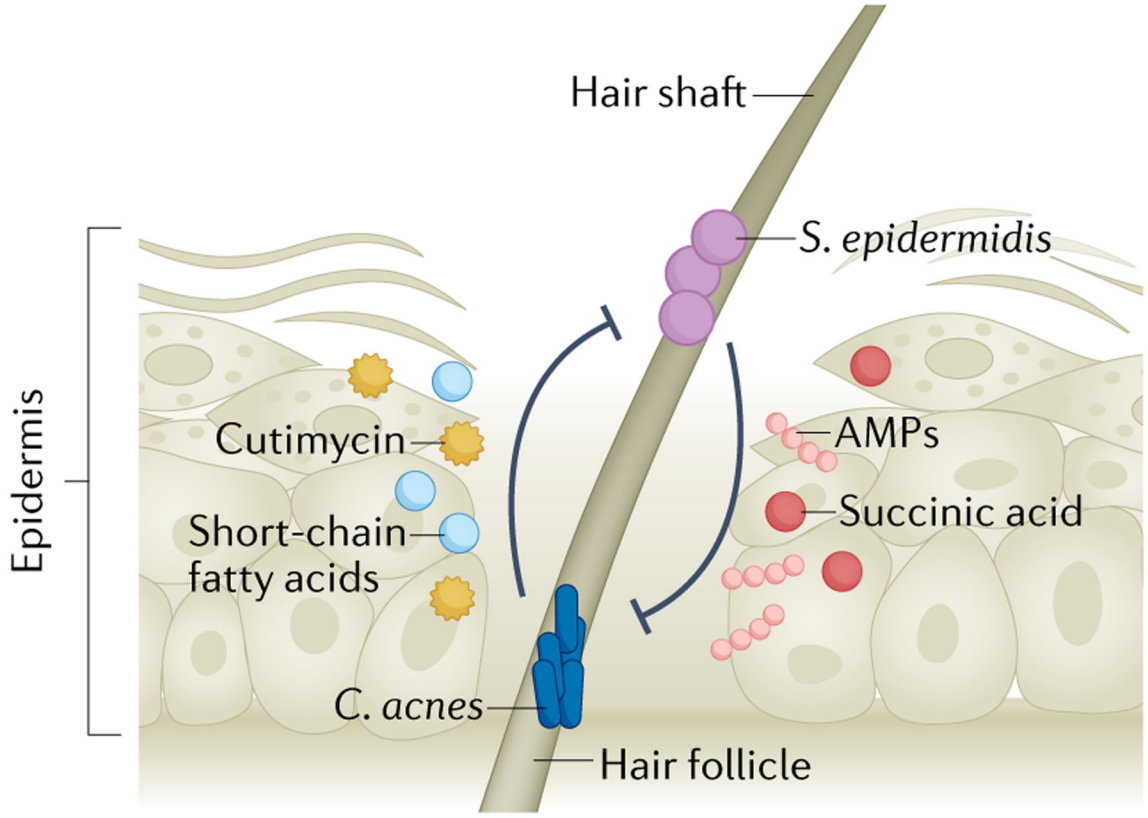


Fig. 4 |. *Staphylococcus epidermidis* competes with *Cutibacterium acnes* in the hair follicle. *Cutibacterium acnes* is a dominant hair follicle colonizer, and its expansion is correlated with progression of the common skin disease acne vulgaris. *C. acnes* encounters and competes with follicle-resident *Staphylococcus epidermidis* through production of the antimicrobial peptide (AMP) cutimycin. *C. acnes* inhibits *S. epidermidis* biofilm formation and sensitizes *S. epidermidis* to antibiotic killing through production of several short-chain fatty acids. *C. acnes* strains may produce other AMPs but this remains unclear. *S. epidermidis* counters this competition through production of AMPs and fermentation of follicle-available glycerol to multiple short-chain fatty acids, including acetic acid, butyric acid, lactic acid and succinic acid, to suppress *C. acnes* overgrowth. *S. epidermidis* strains may also utilize an ESAT6 secretion system to compete with *C. acnes* (not indicated), but this remains to be experimentally determined.

Table 1 |

Staphylococcus epidermidis and its molecular products in therapeutic applications

Application	Treatment	Description	Refs.
Prebiotic	Sucrose	Increased *Staphylococcus epidermidis* fermentation and production of short-chain fatty acids, which inhibit *Cutibacterium acnes*	147
	Poly(ethylene glycol) dimethacrylate	Increased S. *epidermidis* fermentation and production of short-chain fatty acids, which inhibit MRSA	167
	Colloidal oat[a]	Increased S. *epidermidis* growth, lactic acid production Increased lactic acid levels on moderate to severe dry skin of human volunteers	168
	Lactobacillus brevis[a]	Topically applied cream extract promoted S. *epidermidis* growth and improved skin barrier function in human volunteers	163
Probiotic	Alanine auxotroph	Colonization of human skin explants maintained by addition of alanine Proposed for future clinical studies given safety and no requirement for antibiotics	161
	AMP stimulator	Skin and nasal keratinocyte AMP stimulation to inhibit pathogen colonization and/or infection	Skin[59, 64]
		High dependency on which S. *epidermidis* strain is applied	Nose[153]
	Co-application[a]	*Staphylococcus hominis* and S. *epidermidis* lantibiotic strains in formulated lotion decreased S. *aureus* colonization in atopic dermatitis lesions of human volunteers	130
	Esp producer[a]	Nasal S. *aureus* decolonization in human volunteers	154,155
	6-HAP producer	Strain-dependent expression, reduced tumour incidence in mice exposed to repeated ultraviolet B radiation	52
Postbiotic	Lyophilized bacteria[a]	Strains isolated from patients, lyophilized and reapplied in cream Increased skin hydration and lipid content in human volunteers	159
	Bacteriocins and lantibiotics	Selective host range to kill pathogens, but not clinically validated	132,136,169
	Proteases	Esp protease inhibited S. *aureus* biofilm	Esp[154,155]
		Sphingomyelinase increased skin barrier hydration, and expression was detected on arms/faces of human volunteers	Sphingomyelinase[46]
	Small molecules	6-HAP inhibited tumour proliferation	6-HAP[52]
		AIPs decreased S. *aureus* virulence	AIPs[124,125]
		6-Thioguanine inhibited S. *aureus* purine biosynthesis	6-Thioguanine[139]

6-HAP, 6-*N*-hydroxyaminopurine; AIP, autoinducing peptide; AMP, antimicrobial peptide; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a]Treatment has been performed on human volunteers.