INTRODUCTION

The skin harbours a huge composition of various living microorganisms, the skin microbiota. There is increasing evidence that the skin microbiota with its multifaceted pattern of diverse microbial species, the microbiota members, contribute to skin homeostasis. Accordingly, a dysregulation in the fine-tuned balanced microbiota system may enhance the susceptibility for skin diseases.\(^1\,^2\) To keep the microbiota in the preferred status, specific regulatory mechanisms are needed that control and shape the microbiota. In this regard, host antimicrobial peptides (AMPs) may have a profound influence on the composition of the microbiota. AMPs are small proteins and peptides that exhibit direct antimicrobial activity in low concentrations against various microorganisms.\(^3\,^4\) In addition, many AMPs function also as immunomodulators and can exert anti- and pro-inflammatory activities.\(^5\) The antimicrobial capacity of AMPs together with their epithelial expression makes it likely that they directly interact with the microbiota due to their antimicrobial activity. Thus, AMPs may have developed during evolution as important regulators and shapers of the microbiota. The correctness of this hypothesis has been impressively shown by transgenic overexpression of only one human AMP, human defensin (HD)-5, in the mice paneth cells of the small intestine. This resulted in marked changes in microbiota composition.\(^6\) In addition, it seems that the anaerobic milieu in the gut enhances the activity of the AMP human beta-defensin (hBD)-1 by reduction of the disulfide bonds. Reduced hBD-1 became...
a potent AMP against anaerobic gut commensals. Moreover, there is increasing evidence that other AMPs such as RegIIIγ and its human counterpart HIP/PAP8 and the cathelicidin LL-37/CRAMP9 contribute to maintain the gut microbiota balance.

In contrast to the gut, the impact of AMPs on the skin microbiota is less explored but an increasing number of studies strengthen the hypothesis that skin-derived AMPs may have a crucial impact on the cutaneous microbiota. In the following, we will discuss this hypothesis in detail.

2 SKIN-DERIVED AMPs

Skin-derived AMPs are characterized by a wide-ranging killing potential against microorganisms. The first described AMP in human skin is lysozyme.10 In 1997, Harder et al. isolated the first AMP from human skin from lesional scales of psoriasis patients. Because of its structural similarity to the 3 to 5 kDa cationic β-defensins from bovine epithelia, it was called human β-defensin-2 (hBD-2).11 Defensins typically have β-sheet structures and six cysteine residues, which are connected by three intramolecular disulfide bridges. Based on the position of the disulfide bridges, a distinction is made between α- and β-defensins.12 The expression of hBD-2 can be induced by cytokines and bacteria.13 HBD-2 exhibited high activity against Gram-negative bacteria such as Pseudomonas aeruginosa and Escherichia coli as well as against the yeast Candida albicans. In 2001, another beta-defensin, hBD-3, was also isolated from psoriatic skin.15 HBD-3 is an AMP with a very broad range of activity, and it acts in low doses and remained effective even in high salt concentrations.15 Another inducible AMP is encoded by the CAMP (cathelicidin antimicrobial peptide) gene. It encodes for an 18 kDa precursor which is proteolytically processed to a 37 amino acid containing peptide, termed LL-37. LL-37 is the only human cathelicidin, and it is also expressed in the skin.16 LL-37 shows broad antimicrobial activity against Gram-positive and Gram-negative bacteria, fungi including yeasts. In contrast to hBD-2, hBD-3 and LL-37, which are only weakly expressed in healthy skin, Gläser et al. identified the S100 protein psoriasin (S100 A7) as abundant AMP of healthy skin.19 Psoriasis exhibits antimicrobial activity especially against E. coli, and its reduced form has been reported to be active against various fungi.20 Psoriasin was upregulated in chronic wounds21 and psoriasis,22 and its expression in keratinocytes can be induced by pro-inflammatory cytokines.23 Harder et al. isolated a new AMP from the stratum corneum of healthy skin with high antimicrobial activity against a wide range of microorganisms. Because of its structural similarity, this AMP was assigned to the ribonuclease A superfamily and referred to as ribonuclease 7 (RNase 7).24 RNase 7 is a cationic, lysine-rich 14.5 kDa protein with a broad spectrum of antimicrobial activity and very potent ribonuclease activity. RNase 7 is abundant in human skin, and its expression can be further induced by pro-inflammatory cytokines and bacteria.24-28

There is no orthologue in mice, making it difficult to conduct in vivo studies on RNase 7.29 It is a typical characteristic of all the above-mentioned AMPs that they are cationic and therefore positively charged which favours the affinity to the negatively charged bacterial surface. Therefore, it was a surprising finding that dermcidin (DCD), an AMP exclusively secreted by sweat glands, has a negative charge. Nevertheless, it also displays antimicrobial activity by membrane interaction with various microorganisms.20,21

Table 1 summarizes the principal skin-derived AMPs discussed above. It should be noted that additional peptides and proteins with antimicrobial activity are found in skin. Examples are protease inhibitors such as secretory leukocyte proteinase inhibitor (SLPI) and elafin, hornerin-derived cationic intrinsically disordered antimicrobial peptides (CIDAMPs)22 and calprotectin (S100 A8/9). A recent study reported expression of human resistin (hRETN) in the epidermis and showed antimicrobial activity against skin-relevant bacteria suggesting that resistin may also contribute to antimicrobial defence of the skin. Interestingly, there is also evidence that resistin expression is induced by vitamin A, a finding that may help to explain why vitamin A deficiency in humans results in increased susceptibility to skin infection.23 Vitamin-dependent regulation of AMPs is also known for LL-37 which is induced by vitamin D.24 AMPs exhibit also a wide spectrum of immunomodulatory functions. They exhibit own chemotactic activity, enhance chemotaxis of immune cells and trigger immune cell differentiation and maturation of dendritic cells. Furthermore, AMPs mediate the release of pro- and anti-inflammatory cytokines and reactive oxygen species. In addition, AMPs are able to bind and inactivate bacterial endotoxins, stimulate angiogenesis and enhance wound-healing.

Most studies dealing with the antimicrobial activity of AMPs are based on experiments documenting in vitro activity of a specific AMP against microorganisms. However, to address the physiological impact of the AMPs, functional studies are necessary. Several studies have been performed that document the functional impact of AMPs to control the growth of microorganisms. For example, the in vivo inactivation of psoriasin on the skin surface enhanced the outgrowth of applied E. coli. Antibody-based inactivation of RNase 7 revealed its crucial role to control cutaneous growth of S. aureus, Corynebacterium amycolatum, Enterococcus faecium and Pseudomonas aeruginosa. Antibody-based neutralization of hBD-3 revealed an important role of hBD-3 to restrict S. aureus growth.

2.1 AMPs and skin diseases

Despite the fact that AMPs protect our skin, several studies have hypothesized that AMPs could also actively contribute to the pathogenesis of various skin diseases. Increasing evidence for a pathophysiologival role of AMPs has already been shown in psoriasis vulgaris, atopic dermatitis (AD), acne vulgaris, hidradenitis suppurativa, rosacea and wound healing. Small studies or reports exist for nearly all kinds of inflammatory or infectious skin diseases. Importantly, AMPs may not only act as antimicrobial agents but also as pro- or anti-inflammatory molecules, sometimes referred to as a double-edged sword. Table 2 provides an overview of the contribution of AMPs in important skin diseases.
2.1.1 | Psoriasis vulgaris

The human beta-defensins-2 and human beta-defensins-3 (hBD-2 and hBD-3) were firstly detected and isolated from psoriatic scales.\(^{11}\) Meanwhile, numerous AMPs were shown to be overexpressed in the epidermis of psoriasis vulgaris patients.\(^{11}\) It is a clinical and evidenced observation that skin infections are rare in psoriasis. Many AMPs such as hBDs, S100-proteins, LL-37 and RNase 7 are induced in lesional and in non-lesional skin compared to healthy controls.\(^{43}\) They were shown to be upregulated mainly by Th1- and Th17-derived pro-inflammatory cytokines.\(^{44}\) The S100-proteins S100 A7 (psoriasin) and S100 A8/A9 (calprotectin) were shown to induce keratinocyte differentiation, whereas the S100 A8/A9 complex is able to suppress keratinocyte proliferation.\(^{45}\) AMPs may also play a role in the susceptibility and manifestation of psoriasis. People with more than 5 β-defensin copies have a fivefold increased risk of getting the disease than people with only two copies.\(^{46}\) It is believed that the pro-inflammatory activity of the β-defensins, especially hBD-2, may trigger the disease.

2.1.2 | Atopic dermatitis

In contrast to psoriasis, patients with AD often suffer from skin infections mainly caused by *Staphylococcus (S.) aureus* or by Herpes viruses.\(^{47}\) Regardless, it was shown that in contrast to healthy skin, several AMPs were induced, but in comparison with psoriasis skin, they were less enhanced.\(^{48}\) The defective innate barrier in patients with AD may be due to the Interleukin (IL)-4, IL-10 and IL-13 environment of these Th2-derived cytokines.\(^{49}\)

2.1.3 | Acne vulgaris

The pathogenesis of acne includes besides increased sebum production, inflammation and abnormal keratinization the colonization with *Cutibacterium* (formerly *Propionibacterium*) acnes. In lesional skin, increased expression of hBD-2, S100 A7, human neutrophil peptide (HNP) 1–3 and granulysin has been reported.\(^{50}\) In contrast, the expression of dermcidin (DCD) has been shown to be reduced in the sweat of acne patients.\(^{51}\)

2.1.4 | Hidradenitis suppurativa (HS)

Recent research has led to greater insight into the mechanisms involved in HS. Follicular occlusion, follicular rupture, a foreign body-type immune response, a specific genetic signature and environmental factors (e.g. microbial colonization) contribute to the HS phenotype.\(^{52}\) AMPs were shown to be overexpressed in HS lesions as compared with non-lesional skin.\(^{53}\) Psoriasin-mRNA was overexpressed in keratinocytes whereas hBD-2-mRNA was produced mainly by dermal macrophages, leading to a relative deficiency of
hBD-2 in the epidermis of HS lesions. Emelianov et al. identified enhanced expression of cathelicidin LL-37, psoriasin and hBD-3 protein in an immunohistological study of HS patients. In contrast, a relative mRNA deficiency of several AMPs was reported by others and discussed to be related to a relative deficiency of IL-22 and IL-20 in HS. The pattern of AMP expression in HS is still unclear.

2.1.5 | Rosacea

The pathophysiology of rosacea involves multiple factors leading to chronic relapsing inflammatory and vascular reactions. A dysregulation of innate and adaptive immune pathways as well as neurovascular changes are suggested. Recent research has shown that especially enhanced expression of cathelicidin is associated with the exacerbation of the disease. Individuals with rosacea express abnormally high levels of cathelicidin in their facial skin and the proteolytically processed forms of cathelicidin peptides found in rosacea were different from those present in healthy individuals.

2.1.6 | Wound healing

Several studies could demonstrate that AMPs are induced in all stages of wound healing, suggesting that they contribute to the wound healing process. Infection is a major factor inhibiting wound healing, and AMPs play a major role in wounding by controlling microbial proliferation. In addition, other AMP characteristics such as modulating the host’s immune response, induction of cell migration and proliferation, promotion of angiogenesis and vascularization help to accelerate wound healing. AMPs like hBD-2 and psoriasin were shown to be induced in the margins of chronic wounds, whereas hBD-3, RNase 7 and LL-37 were not detected. Uptregulation of hBD-2 was reported to be induced in human skin wounds by epidermal growth factor receptor (EGFR) activation and increases keratinocyte cytokine production and migration.

3 | SKIN MICROBIOTA

The human skin with its 1.8 m² surface is colonized by a diverse composition of microbiota - commonly harmless bacteria, fungi and viruses (Figure 1). Different factors and conditions influence the composition and the amount of skin microbiota which follows astonishing regulation mechanisms. These mechanisms contribute essentially to the enormous skin defence system, which surrounds our bodies. Skin microbiota complements the physical barrier function of the skin in an ecological manner. The human skin surface is colonized by different commensal bacteria like Staphylococcus spp., Corynebacterium spp., Cutibacterium spp. and Actinetobacterium spp.61-66 Furthermore, it was described that viruses like polyomavirus, papillomavirus and circovirus are also a part of the skin microbiota and also present in the hair follicle epithelium. The prevalence of the different species is frequently dependent on the skin area and condition. While humid regions like the armpit or skin appendages like sweat glands are commonly populated by staphylococci or corynebacteria other dryer or more lipophilic regions like sebaceous glands or hair follicle are colonized dominantly by Cutibacterium acnes for instance. Fungi colonize the entire skin surface. The most common representative is from the genus Malassezia spp. that is abundant on all core-body and arm sites. A mixed population of Malassezia spp., Aspergillus spp., Cryptococcus spp. and other fungi species is found on the foot sites where fungus-associated infections occur more often.

3.1 | Microbiota and skin diseases

Skin microbiota can affect several aspects of the host such as immunity, epigenetics and the epidermal barrier. Although cause and consequence are usually difficult to discriminate, changes in the skin microbiota clearly play a role in the pathobiology of many types of inflammatory and infectious skin diseases. It is important to keep in mind that the transition from symbiosis to pathogenicity
is a complex process for microorganisms. The emergence of new technologies enables researchers to have a more comprehensive understanding and analysis of skin microbiota by high throughput sequencing. Conflicting results of different studies in the past may come from the lack of standardized sampling and profiling protocols, or to inherent microbial variability across individuals. The present knowledge of microbiota in the pathogenesis of skin diseases will be outlined only in short within the next part, a various number of excellent reviews dealing with this topic are available.

### 3.1.1 Atopic dermatitis

Dysbiosis is a hallmark of AD, and the skin microbiota in AD patients has been investigated by several studies. A lower overall diversity paralleled by the great dominance of *S. aureus* was significantly associated with a higher burden of disease activity and AD flares. Interestingly, site-specific lipid alterations and correlations with the skin microbiota were also reported in AD. The correlation analysis of skin lipid alterations with the microbiota showed that *Staphylococcus* colonization in AD is positively correlated with different ceramide subspecies. It is generally believed that the disequilibrium of skin microbiota in AD is closely related to *S. aureus* colonization. Besides this high abundance of *S. aureus* in AD lesions, patients present with less *Cutibacterium acnes* (*C. acnes*), *Streptococcus*, *Acinetobacter* and *Corynebacterium*.76

### 3.1.2 Psoriasis vulgaris

It was reported by Chang et al., that the proportion of *S. aureus* was closely related to the lesions of psoriasis, whereas the ratio of
### TABLE 3 Activity of major skin-derived AMPs against Staphylococcus strains

| Staphylococcus | Psoriasin | RNase 7 | hBD-2 | hBD-3 |
|----------------|----------|--------|-------|-------|
| S. aureus ATCC 6538 | >4.5 | 0.3 - 0.5 | 3 - 6 | 0.3 - 0.6 |
| S. lugdunensis ATCC 27836 | >4.5 | 0.4 - 0.8 | <0.2 | <0.15 |
| S. warneri ATCC 27844 | >4.5 | 0.1 - 0.2 | <0.2 | <0.15 |
| S. hominis ATCC 29974 | >4.5 | 0.3 - 0.5 | 0.5 - 1.0 | <0.15 |
| S. cohnii ATCC 29970 | >4.5 | 0.4 - 0.8 | <0.2 | <0.15 |
| S. haemolyticus ATCC 12033678 | >4.5 | >3.4 | >1.4 | >0.1 |
| S. epidermidis ATCC 12034048 | >4.5 | >3.4 | >1.4 | >0.1 |
| S. epidermidis 12033936 | >4.5 | >3.4 | >1.4 | >0.1 |
| S. epidermidis 10026928 | >4.5 | >3.4 | >1.4 | >0.1 |

Various Staphylococcus strains (ATCC and clinical skin isolates) were incubated for 3 h in 10 mM sodium phosphate buffer (pH 7.2) containing 1% trypticase soy broth (TSB) with different concentrations of the indicated AMPs. Colony-forming units (CFU) were determined by serial plating and counting after overnight growth. Shown is the lethal dose (µg/ml) required to reduce 90% CFU (LD90).
significantly associated with two dominant but mutually inhibiting bacteria *Cutibacterium* spp. and *Staphylococcus* spp., and bacterial changes were significantly more associated with dandruff severity than fungi.

4 | AMPS: MODULATORS OF THE SKIN MICROBIOTA

Although the impact of skin-derived AMPs on the cutaneous microbiota is still emerging, there is increasing evidence that AMPs may help to shape and balance the microbiota. This is mainly based on the direct antibacterial activity of AMPs towards microbiota members and on the microbiota-regulated AMP expression in the skin. These two aspects will be discussed in the following.

4.1 | AMPs directly control the growth of microbiota members

4.1.1 | Antimicrobial activity of AMPs against commensals

Several studies have shown that LL-37 is able to restrict the growth of *S. epidermidis* in vitro. Interestingly, different activities of LL-37 against *S. epidermidis* have been reported ranging from almost inactive to highly active.89-92 The reason for such different reported activities may be caused by the various not standardized test conditions or due to the known capability of *S. epidermidis* to lower its susceptibility to cationic host AMPs such as LL-37 and beta-defensins as discussed 4.1.2. Besides its direct antimicrobial activity towards *S. epidermidis*, LL-37 has also been reported to inhibit biofilm formation of *S. epidermidis.*90

It has been shown that inhibition of the aryl hydrocarbon receptor (AhR) leads to increased outgrowth of *S. epidermidis* on the surface of human skin explants.73 Since the AhR mediates expression of AMPs, one may speculate that this growth control of *S. epidermidis* is—at least in part—mediated by AMPs, a hypothesis that needs to be proven.

Since studies that analyse the antimicrobial activity of AMPs against skin commensals are rare, we investigated the *in vitro* activity of four major skin-derived AMPs (psoriasin, RNase 7, hBD-2 and hBD-3) against commensal *Staphylococcus* and compared it to the activity against *S. aureus*. The results are shown in Table 3. These data show that RNase 7 and psoriasin, two AMPs abundant and constitutively expressed on healthy skin, are not able to restrict the growth of *S. epidermidis* in vitro. Other commensal *Staphylococcus* and the pathogen *S. aureus* were affected by RNase 7. In contrast to RNase 7 and psoriasin, the inducible AMPs hBD-2 and hBD-3 are able to restrict the growth of *S. epidermidis* (Table 3).

HBD-2 and hBD-3 are only weakly produced by healthy skin but strongly upregulated during infection, inflammation and wounding. The low abundance of hBD-2 and hBD-3 in healthy skin may favour the growth of *S. epidermidis*. However, it is known that *S. epidermidis* is able to cause severe infections such as bacteremia and sepsis.94 In addition, its increased abundance may also cause deleterious effects due to the expression of proteases as reported in AD.95 Thus, induction of hBD-2 and hBD-3 during inflammation/infection and wounding may offer an inducible protection from the potentially harmful effects of *S. epidermidis*.

In skin regions rich in sebaceous glands, the microbiota member *Cutibacterium acnes* is present in high concentrations. Although it is normally involved in maintaining healthy skin, it can also cause infection and inflammation as an opportunistic pathogen.96 It is likely that also AMPs control the growth of *C. acnes* on the skin surface. Indeed, in vitro tests have shown that various AMPs such as LL-37, hBD-2, RNase 7 and psoriasin can restrict its growth.50 *C. acnes* is also an abundant member of the hair follicle microbiota, and various AMPs such as LL-37, psoriasin and RNase 7 are produced by the hair follicle keratinocytes.97 Thus, AMPs may also play an important role to control *C. acnes* growth in the hair follicle niche.97 It remains to be determined if the AMP-mediated growth control of *C. acnes* is impaired in *C. acnes*-associated skin diseases such as acne vulgaris.50

Another abundant member of the cutaneous microbiota is non-diphtheria corynebacteria. Aerobic corynebacteria are implicated in the biotransformation of sweat components in the axillae leading to malodour.98 We could recently show that RNase 7 is induced in keratinocytes exposed to the skin commensal *Corynebacterium amycolatum*. RNase 7 exhibited high antimicrobial activity against corynebacteria, and the capacity of stratum corneum extracts to restrict the growth of *C. amycolatum* partially depended on the activity of RNase 7.99 These data suggest that AMPs also interact with corynebacteria and control their growth on the skin surface.

Although this review focuses on host AMPs, it is noteworthy that microbiota members also produce antimicrobial activity and antimicrobial peptides that may play a crucial role to protect human skin from infection.99-105 There is increasing evidence that such microbiota members are deficient in AD making the AD skin more susceptible for colonization with *S. aureus*.101,103

4.1.2 | Resistance mechanisms of commensals towards AMPs

*S. epidermidis* uses different strategies to protect itself against the potent action of AMPs. One mechanism is the production of the polysaccharide intercellular adhesin (PIA). PIA is an integral essential factor of the extracellular matrix of *S. epidermidis*. Mutants deficient in PIA were more susceptible to LL-37 and hBD-3 as compared to the wild-type.106 Besides acting as a mechanical barrier, PIA may also protect from cationic AMPs through electrostatic repulsion. It is an interesting hypothesis that PIA may contribute to the abundance of *S. epidermidis* on the human skin surface.106 *S. epidermidis* is able to sense the presence of AMPs and activate specific resistance mechanisms towards AMPs. In 2007, the group of Otto and colleagues discovered a novel AMP sensor system in
**S. epidermidis** which they named *aps* (antimicrobial peptide sensor). Deletion mutants of this system showed an increased susceptibility towards hBD-3. Sensing of AMPs by the *aps* system leads to upregulation of two well-described resistance mechanisms of Gram-positive bacteria to cationic AMPs, that is dlt-operon-mediated D-alanification of teichoic acids and MprF-mediated incorporation of lysyl-phosphatidylglycerol in the cytoplasmic membrane. This strategy eventually leads to the repulsion of positively charged AMPs through a reduction of the net negative charge of the bacterial cell envelope.

In Gram-negative pathogens such as *Salmonella* spp., similar sensor systems of cationic AMPs have been described. Activation of this system results in reduction of the negative charge of the lipid A part of the lipopolysaccharide (LPS) molecule. It is likely that similar mechanisms to lower the susceptibility towards AMPs are also used by Gram-negative members of the human skin microbiota.

Another strategy of bacteria to evade AMPs is the secretion of proteases that proteolytically inactivate AMPs. This has been mainly shown for *S. aureus* which secretes several proteases such as V8 protease or aureolysin that inactivate AMPs such as LL-37. Interestingly, the *S. epidermidis* protease SepA (71% identity to *S. aureus* aureolysin) degraded dermcidin and favoured resistance development of *S. epidermidis* towards dermcidin, which was not the case for hBD-3 and LL-37. In general, protease-based inactivation of AMPs may be a general feature of microbiota members to avoid killing by AMPs but this remains to be shown by further research.

Another strategy of skin commensals to avoid killing by AMPs is to switch from the planktonic growth mode into biofilm formation. At least in the nasal epithelium, this seems to be an efficient way how *S. epidermidis* evades the action of AMPs.

Several other strategies may also play a role for AMP resistance development of members of the cutaneous microbiota. Most of such strategies have been detected in pathogenic non-skin-derived bacteria and it remains to be shown if such resistance mechanisms are also utilized by skin commensals. Examples (reviewed in are: (a) Capsular polysaccharides that trap AMPs and hamper AMP interactions with the microbial cell surface; (b) bacterial efflux systems that extrude AMPs from the cell membrane site to the extracellular environment; and (c) bacteria-mediated downregulation of AMPs. This may be through direct inhibition of AMP synthesis or indirectly by induction of host proteases that cleave and inactivate AMPs as it has been shown for *P. aeruginosa* which induces cathepsins in the lung epithelium leading to inactivation of hBD-2 and hBD-3.

### 4.2 Control of AMP expression by the cutaneous microbiota

It is not surprising that the members of the cutaneous microbiota and their secreted products are sensed by host keratinocytes and immune cells. The microbiota-mediated activation of these cells leads to a concerted modulation of the expression of a variety of genes. A complete picture has recently been provided by Meisel and colleagues who profiled the skin transcriptome of mice reared in the presence or absence of microbiota. A total of 2820 genes were differentially expressed thus documenting the crucial impact of the microbiota on skin physiology. Many genes involved in the immune and inflammatory response were upregulated. Since this resulted not in detectable inflammation, a fine-tuned regulatory network must exist to balance the skin homeostasis. Of note, also the gene expression of several AMPs was upregulated indicating that the microbiota contributes to provide the skin with a constant antimicrobial shield due to the presence of AMPs.

When investigating the interplay between the microbiota and AMPs, it is important to consider that human skin harbours a different microbiota composition than mouse skin and that human skin produces a different set of AMPs, that are either not present in mice skin (eg RNase 7) or differentially regulated. Thus, it is important to analyse the microbiota-AMP interplay directly in a human setting. Many studies used cultured keratinocytes that were stimulated with specific microbiota members. Most reports in this context deal with *S. epidermidis* because it is one of the most abundant culturable skin commensals. Stimulation of keratinocytes with *S. epidermidis* or its secreted factors induced the expression of many AMPs such as the ß-defensins hBD-2 and hBD-3 or RNase 7 (and own unpublished results). *S. epidermidis* induced the expression of hBD-2 and hBD-3 also in 3D skin models and skin explants. In line with the data obtained with skin keratinocytes, stimulation of human nasal keratinocytes with *S. epidermidis* upregulated the expression of hBD-3, RNase 7 and LL-37.

Mechanistically, induction of hBD-2 and hBD-3 by *S. epidermidis* was mediated by a small *S. epidermidis*-derived lipopeptide that activated Toll-like receptor-2 (TLR-2) and subsequently the p38 MAP kinase pathway. Besides TLR-2, also the epidermal growth factor receptor (EGFR) and the transcription factor NF-kappaB have been implicated in the *S. epidermidis*-mediated induction of beta-defensins and RNase 7. Interestingly, the induction of hBD-3 and RNase 7 by *S. epidermidis* was synergistically amplified in the presence of *S. aureus* which highlights a potential mechanism of how skin commensals such as *S. epidermidis* amplify the innate immune response in the presence of an infection. Moreover, there is some evidence that *S. epidermidis* induced hBD-3 in a 3D epidermal equivalent via activation of the AhR. Similarly, activation of the AhR by coal tar in an epidermal equivalent induced expression of hBD-2 and other AMPs. Together, these data support a previously unappreciated contribution for the AhR in cutaneous defence.

The question arises how *S. epidermidis* avoids killing by AMPs that were induced by itself. As discussed above, one reason may be an adaptation due to specific resistance mechanisms towards the killing activity of AMPs. Another mechanism may the interference with host signal transduction. We could recently show that *S. epidermidis* induced the host regulator protein A20 in human keratinocytes. A20 is an inhibitor of NF-kappaB, and A20 inhibited the *S. epidermidis*-mediated induction of IL-1beta and hBD-2 in keratinocytes. Thus, *S. epidermidis* exploits a host regulator protein A20 to attenuate induction of cutaneous defence molecules such as AMPs.
and cytokines, which may help S. epidermidis to persist as a commensal on human skin.\textsuperscript{117}

The Gram-negative bacterium Roseomonas (R.) mucosa is a member of the healthy skin microbiota, and its absence in AD may trigger the disease.\textsuperscript{103,126} Accordingly, cutaneous treatment of AD patients with R. mucosa lowered the disease severity and S. aureus burden.\textsuperscript{126} Interestingly, R. mucosa induced the expression of hBD-2 and LL-37 in keratinocytes suggesting that the induction of AMPs may also be related to its beneficial effects when used to treat AD patients.\textsuperscript{103} Similarly, specific anaerobe bacteria such as Finegoldia spp. have been reported to induce AMPs in keratinocytes. A low presence of such bacteria, as seen in AD, may decrease cutaneous defence.\textsuperscript{127,128}

LL-37 and hBD-2 are induced in acne lesions. This may be related to the fact that Cutibacterium acnes is able to induce the expression of hBD-2 and LL-37 in keratinocytes.\textsuperscript{50} It is still not clear if the induction of LL-37 and hBD-2 by C. acnes serves always as a beneficial protection step or may trigger in specific circumstances (e.g. in acne vulgaris) an inflammatory scenario due to the immunomodulatory activities of these AMPs.\textsuperscript{30}

The above-mentioned studies clearly document that members of the cutaneous microbiota induce the expression of various AMPs. As discussed in \textbf{4.1.}, inducible AMPs such as hBD-2 and hBD-3 are able to restrict the growth of commensal Staphylococci. In addition, Corynebacteria induce RNase 7 and are controlled by RNase 7. As mentioned, LL-37 and hBD-2 are active against C. acnes and their expression is induced by C. acnes. This highlights the presence of a feedback loop that regulates the fine-tuned AMP-microbiota homeostasis: The microbiota induces the expression of AMPs, this leads to an enhanced AMP-mediated growth control of the microbiota, and this results in a decreased microbiota abundance that is followed by a declined induction of AMPs. Lower level of AMPs in turn promotes growth of the microbiota (Figure 2).

Further evidence for the crucial role of the microbiota-AMP interaction has been recently reported in a mouse model. Mice deficient in cutaneous expression of the antimicrobial resistin-like molecule RELM\textsubscript{α} showed an altered skin microbiota composition, and cutaneous expression of RELM\textsubscript{α} was induced by the microbiota. These data indicate that mouse RELM\textsubscript{α} shapes the composition of the skin microbiota and makes it likely that the human antimicrobial resistin may also participate in shaping the skin microbiota.\textsuperscript{36}

\section{Therapeutic Concepts}

It is becoming increasingly clear that the skin microbiota offers a rich number of opportunities for the development of novel therapeutics to improve skin health and treat skin infections. A lot of research activities in the last years have documented that specific skin diseases are associated with a decreased microbiota diversity with specific, potentially beneficial members being underrepresented. The documentation of successful approaches to modulate the gut microbiota through faecal transplants\textsuperscript{129} raised the possibility that transplantation of beneficial microbiota members onto the skin offers a promising strategy to support the treatment of inflammatory and infectious skin diseases.\textsuperscript{7,130} Such bacteria are believed to have a beneficial influence on skin health by modulating the immune system (including production of AMPs), curbing inflammation and providing own killing activity that displaces potential pathogenic microorganisms such as S. aureus in AD. In this regard, it has been reported that specific bacteria that are able to restrict the growth of S. aureus are underrepresented in AD. Examples are coagulase-negative staphylococci such as S. epidermidis and S. hominis that produce bacteriocins targeting S. aureus. Topical application of such strains to the diseased skin of AD patients decreased colonization by S. aureus.\textsuperscript{101} Similarly, an association of low abundance of specific Gram-negative bacteria such as Roseomonas mucosa and AD has been reported.\textsuperscript{103} Indeed, topical treatment of AD patients with R. mucosa was associated with a decline of S. aureus colonization and an overall improvement of disease symptoms.\textsuperscript{126} The use of specific microorganisms such as S. epidermidis or the yeast Malassezia spp. that have been reported to produce proteases with anti-biofilm properties against S. aureus may also be beneficial for skin health in the context of AD.\textsuperscript{104,131}

Rather than applying only one specific strain, one may speculate that a cocktail of different strains individually adapted to the personal recipients’ disease situation offers therapeutic advantages. Paetzold et al. used a mixture of specific C. acnes strains taken from healthy donors skin and documented that transplantation of three C. acnes strains has synergistic effects on colonization of the healthy recipient’s skin. This study highlights the possibility to develop specific probiotic solutions based on the healthy skin microbiota that

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{feedback_loop.png}
\caption{Feedback loop of skin microbiota and AMPs. Skin microbiota is able to induce AMPs. This causes a growth control mechanism of the persistent skin microbiota. Low microbiota levels imply lower AMP levels and killing activity that result in an outgrowth of the microbiota.}
\end{figure}
may help to revert a diseased microbiota state to a more healthy one.132

In addition to the application of skin-derived commensals, several studies have also reported the successful use of probiotics containing non-skin-derived probiotics (eg lactic acid bacteria) to treat skin diseases such as AD or acne vulgaris.133,134 It is likely that most of these bacterial treatments are associated with a modulation of AMPs and this may contribute to the beneficial effects. In addition, other strategies that utilize AMP inducers such as vitamin D3135 or application of a urea-containing ointment136 may exploit the beneficial effects of AMPs on the microbiota. However, one has to keep in mind that there is increasing evidence that overexpression of specific AMPs may trigger skin inflammation as reported for hBD-2 in psoriasis.46,137,138 and for LL-37 and its proteolytic derivatives in rosacea.57 Moreover, we do not know which AMPs at which distinct skin area and at which concentrations are favourable for skin homeostasis. This demands the need to increase our insight into the role of AMPs in skin biology and as potential therapeutics.

6 | CONCLUSION

Despite a lot of research in the last two decades, our knowledge about the role of AMPs to maintain skin homeostasis and to shape the cutaneous microbiota is still very limited. As highlighted in this review, many studies suggest that AMPs may have a profound influence on the skin microbiota. It is intriguing to speculate that besides protecting the skin from pathogens, an evolutionary ancient major role of AMPs is to control and shape the cutaneous microbiota. Clearly, more functional and association studies are needed to gain more insight into the AMP-microbiota interaction.

CONFLICT OF INTEREST

The authors declare no conflicting results.

AUTHOR CONTRIBUTIONS

F.R., R.G. and J.H. wrote the manuscript. All authors have read and approved the final manuscript.

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