Skin Pharmacology and Physiology

Antimicrobial Peptides and Skin: A Paradigm of Translational Medicine

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Abstract

Antimicrobial peptides (AMPs) are small, cationic, amphiphilic peptides with broad-spectrum microbicidal activity against both bacteria and fungi. In mammals, AMPs form the first line of host defense against infections and generally play an important role as effector agents of the innate immune system. The AMP era was born more than 6 decades ago when the first cationic cyclic peptide antibiotics, namely polymyxins and tyrothricin, found their way into clinical use. Due to the good clinical experience in the treatment of, for example, infections of mucus membranes as well as the subsequent understanding of mode of action, AMPs are now considered for treatment of inflammatory skin diseases and for improving healing of infected wounds. Based on the preclinical findings, including pathobiochemistry and molecular medicine, targeted therapy strategies are developed and first results indicate that AMPs influence processes of diseased skin. Importantly, in contrast to other antibiotics, AMPs do not seem to propagate the development of antibiotic-resistant micro-organisms. Therefore, AMPs should be tested in clinical trials for their efficacy and tolerability in inflammatory skin diseases and chronic wounds. Apart from possible fields of application, these peptides appear suited as an example of the paradigm of translational medicine for skin diseases which is today seen as a 'two-way road' – from bench to bedside and backwards from bedside to bench.

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Introduction

Antimicrobial peptides (AMPs) are also known as host defense peptides. More than 1,200 AMPs from different origins – bacteria, plants, insects, reptiles and mammals – have been reported [1–3]. The 'nature's antibiotics' form the first line of mammalian host defense against pathogens due to an important function as effector agents of the innate immune system [5]. Recent evidence suggests that AMPs also play an important role as signaling molecules in linking innate and adaptive immune responses [6, 7].

The small, cationic, amphiphilic peptides built up by 6–50 amino acids [1, 4] interact with anionic phospholipid membranes [4, 8] and thus show a broad-spectrum microbicidal activity against both bacteria and fungi [4].
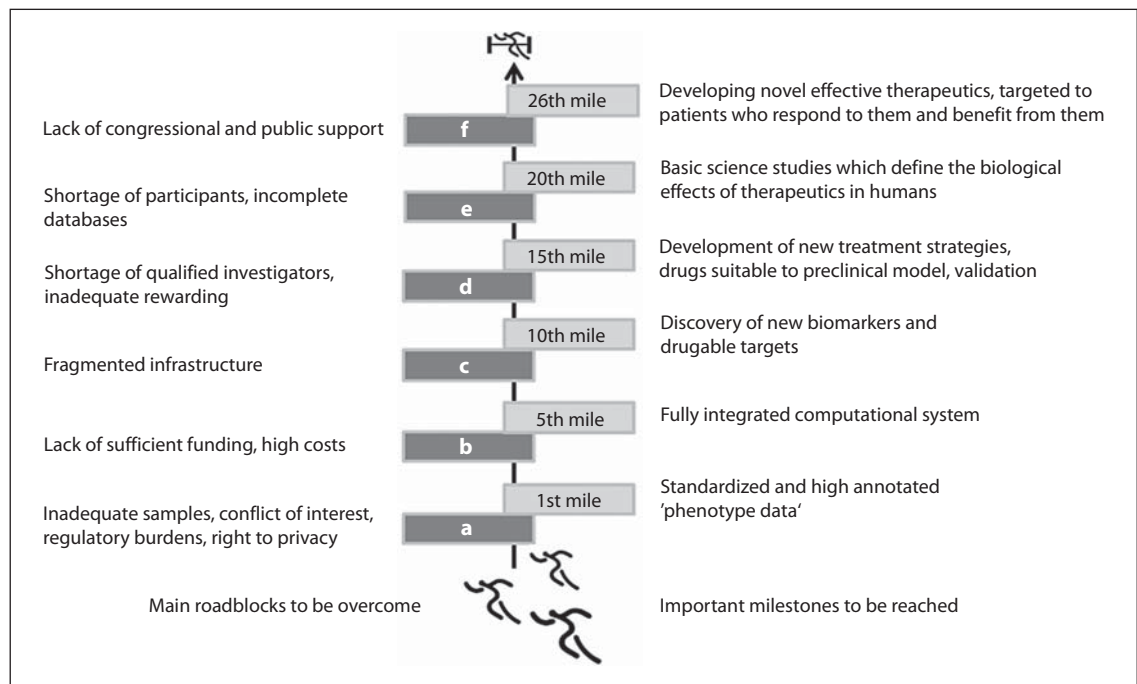
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Fig. 1. Milestones of turning laboratory findings into therapy (modified from Kotlan et al. [14], with permission).

By directly targeting and destroying membranes even in multidrug-resistant pathogens [9], AMPs might contribute to overcoming the growing problems of antibiotic resistance [1, 9, 10], and the shortage of new antibiotics to combat multidrug-resistant microbes has led to a new interest in AMPs at large and, in particular, to a renewed interest in older AMPs like polymyxins and tyrothricin [12]. In particular, AMPs as multifunctional agents [13] might provide new approaches in the management of infectious/inflammatory skin diseases and thus belong to the biggest hopes in curative dermatology.

AMPs are also well suited as an example of the paradigm of translational medicine, which means to introduce novel, effective therapeutic strategies in the clinic [14] by effectively translating basic research discoveries into clinical tools [14, 15]. Thus, translational medicine is the interface between preclinical research and clinical development. The course of translational medicine was seen as a one-way street – with the goal of reaching the path 'from bench to bedside' as quickly as possible [14, 16] – although it soon became evident that the transfer of knowledge from the preclinical to the clinical grounds does not often function smoothly. This is partly due to the fact that even if preclinical research is being conducted on a large scale today, the results are sometimes ignored [16] and/or cannot be transferred from test tube or animal model to human diseases in real life [17]. Moreover, various regulatory obstacles and difficulties impede knowledge transfer ([14]; fig. 1). Recently, it has also been realized that new insights gained from observations on clinical grounds should flow back to the laboratory to develop new observation-based therapy strategies [14]. As a result, today, translational medicine is no longer seen as a one-way street but rather as a 'two-way road' – from bench to bedside and backwards from bedside to bench [14, 18].

From a chronological point of view, these two paths can also be seen in the development of AMPs for the treatment of skin diseases. For example, in the past, there already were individual peptides which, after their discovery and characterization, quickly and easily found their way from the laboratory to clinical application ('from bench to bedside') and today – decades after their identification – are still being used successfully. According to results of current investigations into molecular pathophysiology of skin diseases such as psoriasis, eczema or infected wounds, AMPs such as magainins isolated from African clawed frog *Xenopus laevis* and protecting the frog's skin against infections with bacteria

and fungi, may allow the rear-entry path 'from bedside to bench' – from clinical back to preclinical investigations [19–22].

For other AMPs, researchers try to gain a better understanding of their role in the human skin and in skin diseases in advance to possibly be able to use their therapeutic potential in a targeted manner. As of today, it is already tempting to imagine that, in the future, the forward-looking 'from bench to bedside' path will become more important again. This is not only due to the fact that preclinical research activity in the area of skin diseases will continue to be more effectively organized, but also to the fact that all parties involved in the development of topical medicaments – basic scientists, pharmacologists, pharmacists, clinicians, ethic philosophers, patient advocates and not least the regulatory agencies – are working increasingly hand in hand today. As a result, many obstacles in the transfer from preclinical to clinical expertise tend to be removed during the preliminary stages.

From Bench to Bedside: The Past

Historically, the AMP era was born more than 6 decades ago when cationic cyclic peptide antibiotics, namely polymyxins and tyrothricin, were discovered and found their way into clinical application relatively quickly, though their modes of action were only uncovered years or even decades later. These AMPs had been somewhat forgotten as a result of the discovery of classical antibiotics such as penicillin before they currently began to experience a comeback in light of the increasing resistance problem vis-à-vis classical antibiotics and the extreme difficulty in developing truly novel antibiotics [23].

Polymyxins were discovered in 1947 in different species of *Bacillus polymyxa* [24]. Only two of them, polymyxin B and E (colistin), have been used in clinical practice. Polymyxins are pentabasic decapeptide antibiotics which contain a cycloheptapeptide ring with a C9 or C10 fatty acid chain through an α-amide linkage. Polymyxins are active against Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Enterobacter* species even if they are multidrug-resistant. The target of antimicrobial activity is assumed to be the bacterial membrane, but there are also data supporting a multi-hit hypothesis. Polymyxins have also been shown to be an inhibitor of a single subunit NADH dehydrogenase (NDH-2) and quinol oxidases from certain bacteria making these AMPs promising chemotherapeutic agents [10]. As early reports described
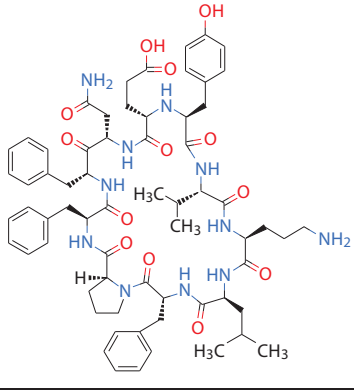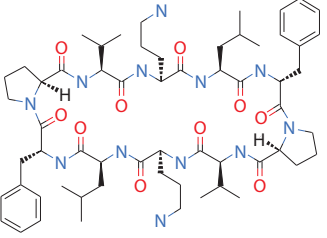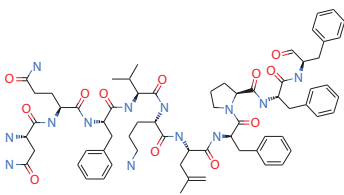
a high incidence of nephrotoxicity and neurotoxicity [25, 26], polymyxins were gradually withdrawn from clinical practice in the 1970s as newer antibiotics with the same or a broader antibacterial spectrum considered to be less toxic were introduced [12, 27]. In recent years, we have observed a renewed interest in polymyxins supposedly due to AMPs' bactericidal activity even against multidrug-resistant bacteria by perturbing membrane integrity and due to actually less frequent and severe toxicity of polymyxins than originally reported. Moreover, a more careful dosing and the use of critical care services allows for risk control [27].

In clinical use, for decades also tyrothricin has gained particular interest for the topical treatment of superficial infectious skin wounds. Just as polymyxin, tyrothricin's potential was slightly underestimated over the years. Produced by *Bacillus brevis* [28], this polypeptide antibiotic consists of the two cyclic decapeptides, gramicidine S (22%) and tyrocidine A (78%) [29] (fig. 2), both peptides commanding broad bactericidal activity against Gram-positive bacteria due to intercalation of the peptides into bacterial membranes. This leads to the formation of hydrophilic ion channels rapidly causing cell leakage and cell death [30]. The antimicrobial efficacy of tyrothricin seems to be the result of synergistic effects of tyrocidine (amino acids, purines, pyrimidines and phosphates) and gramicidine (increased potassium outflow) [31]. In addition, gramicidin disrupts vital functions of the bacterial cell by uncoupling the phosphorylation of the respiratory chain [31].

More recent publications have shown that tyrothricin in vitro shows a clinically relevant antibacterial activity against Gram-positive bacteria isolated from the normal flora of the respiratory tract with minimal inhibitory concentrations (MIC_{90}) ranging from 0.046 mg/l for *Streptococcus pyogenes* to 3.12 mg/l for *Staphylococcus aureus*, methicillin-susceptible (MSSA) and – particularly noteworthy – methicillin-resistant and multidrug-resistant strains of *S. aureus* [32, 33]. In vitro, tyrothricin is also active against streptococci including enterococci [32, 34] and yeasts like *Candida albicans* [35].

Besides its antibacterial activity, tyrothricin is also able to inactivate viruses like Sendai virus [36], herpes simplex virus (HSV) [37] and human immunodeficiency virus (HIV) [38]. Toxicity towards eukaryotic cells [39] restricts the use of tyrothricin as antibiotic to local application [40], in particular for the treatment of infected skin and infected oropharyngeal mucous membranes.

In the treatment of infectious small, superficial wounds, tyrothricin may find its place; also, resistance

Substance	Tyrothricin	Gramicidine	Tyrocidine A
Structural formula			
Molecular weight	1,228.44 (g/mol)	1,141.45 (g/mol)	1,254.48 (g/mol)
Empirical formula	$C_{65}H_{85}N_{11}O_{13}$	$C_{60}H_{92}N_{12}O_{10}$	$C_{66}H_{87}N_{13}O_{12}$

Fig. 2. Tyrothricin, gramicidine and tyrocidine.

development to tyrothricin seems to be a rare event [34]. For example, the prolonged use of tyrothricin tooth paste over 2 years by 99 subjects neither led to an increase in the numbers of tyrothricin-resistant microorganisms nor to an increase in cross-resistance to penicillin, streptomycin, tetracyclines and chloramphenicol [41]. A recent study has demonstrated that Gram-positive bacteria including staphylococci and streptococci (including enterococci), as well as *Corynebacterium* spec. and yeast species, namely *C. albicans* and *Candida parapsilosis,* still turn out to be highly susceptible to tyrothricin, and susceptibility of formerly sensitive Gram-positive bacterial and yeast strains could be preserved over the years, indicating that the risk of resistance development against topically applied tyrothricin is negligible (unpublished data Engelhard). Microbiological data are in accordance with clinical data. In detail, the efficacy and tolerability of an antiseptic wound powder based on tyrothricin was demonstrated in a prospective, randomized multicenter trial with 131 patients with posttraumatic and surgical cutaneous lesions. Tyrothricin powder proved superior to vehicle concluding from the radius of the lesions (p = 0.016) as well as the wound index (p = 0.005), while the tolerability of verum and vehicle did not differ [42]. Pertinent findings together with the lacking evidence for the development of resistance are reflected by the drug approval for topical formulations incorporating tyrothricin 0.1% (Tyrosur® Puder/Gel) for bacterially superinfected superficial wounds due to susceptible microorganisms. This is a good example of how an 'old' medicament can still be used and, in fact, is still being used today to treat skin diseases – even though initially the exact mode of action was not known.

From Bedside to Bench: The Present

Reflecting the good clinical experience with the use of 'old' AMPs such as tyrothricin and the subsequent understanding of their mechanisms of action, the potential of the 'natural antibiotics' at large has come into focus with respect to the treatment of infectious skin diseases. Owing to the significantly improved possibilities of molecular medicine, AMPs' immunomodulatory effects on the innate immune system and the adaptive immune response have been revealed, and AMPs thus might be used to treat inflammatory skin diseases at large and, in particular, to improve wound healing. Because of the new understanding of translational medicine as a 'two-way road' and because of the many regulatory obstacles and difficulties that currently stand in the way of a transfer of knowledge from the laboratory to the hospital [14], the

first step in dermatology's approach today is understanding the role of AMPs in human skin. Based on these findings, targeted therapy strategies are developed which focus on the mechanism of action. In a third step, the insights gained in preclinical trials are supposed to be put into practice, and the AMPs that modulate the defined disease-related processes will have to be tested in clinical studies for their efficacy and tolerability. The current status of research, however, is an improved understanding of the physiological activity of AMPs in human skin – and thus of their role in infectious and inflammatory skin diseases as well.

AMPs in Invertebrate and Vertebrate Skin

AMPs have been found in bacteria, invertebrates and vertebrates and show activity in organisms with or without complex adaptive immune system [43, 44]. The observation that AMPs are locally produced in the epithelium after invertebrates like the moth *Hyalophora cecropia,* the fruit fly *Drosophila melanogaster* and at least 150 further insects [43, 45] have had contact with microbes supports the hypothesis that AMPs are part of a kind of primary 'chemical' defense system which – in addition to the physical barrier provided by the skin – protects interfaces from infection with pathogenic microorganisms. This hypothesis was supported in the late 1980s when the first inducible AMPs were isolated in vertebrates [19] – for example the AMP magainin. It is secreted in the neuroepithelial glands of the frog's skin upon stimulation with noradrenalin [46]. Magainin commands a wide spectrum of antimicrobial activity against Gram-positive and Gram-negative bacteria and fungi [21], antiviral properties [47] and possibly anti-spermicidal activity [48]. Binding to anionic phospholipids on the outer leaflet of bacterial membranes, magainin leads to perturbation of membrane permeability and subsequently cell lysis [20, 21, 49–52]. Today, magainins and their analogues are promising agents for future therapeutic approaches.

AMPs in Human Skin

Human skin is permanently exposed to microorganisms but rarely infected, thus showing a natural resistance towards pathogens. One, if not the main, reason for this might be the existence of constitutively and inducibly produced AMPs [43]. In fact, human skin is a major source of AMPs [44] with keratinocytes as the main producers [6] as cutaneous AMPs include the main groups of defensins, cathelicidins, dermcidin (DCD) and other small peptides such as neuropeptides and chemokines [44]. For several years, there has been a strong interest in

better understanding the role of constitutively expressed and especially inducible AMPs in infectious/inflammatory diseases to determine their modes of action ('from bedside to bench') with the aim of being able, in the long run, to make targeted use of the therapeutic potential of these peptides in skin diseases ('from bench to bedside'). In the following section, we briefly present the most important human AMPs and subsequently shed light on their role in infectious/inflammatory skin diseases.

Defensins

Human defensins are AMPs of 30–40 amino acids with a molecular weight of about 3–4 kDa; six cysteines form intramolecular disulfide bonds [4]. Defensins can be classified as α-, β- and θ-forms based on their typical spaces between the cysteine residues and their disulfide pattern. Neutrophils express α-defensins [53], whereas keratinocytes are the source for β-defensins [6]. Up to now, six different human α-defensins have been described: HPN (human neutrophil peptide)-1, HPN-2, HPN-3, HPN-4, as well as HD (human defensin)-5 and HD-6, with the latter two only being constitutively produced in Paneth cells (long-lived secretory cells) in the small intestine [54] and actively secreted in the urogenital tract; HD-5 is additionally expressed in female reproductive tissues [55]. To date, four different β-defensins expressed by keratinocytes have been identified and characterized: HBD (human β defensin)-1 to -4 [44]. HBD-2 and -3 are highly induced by Gram-positive bacteria and inducibility of HBD-3 influences the severity of Gram-positive skin infection [56]. θ-defensins were primarily found in non-human primates [57] but have not been identified in humans so far.

Both α- and β-defensins show a broad antibacterial activity against Gram-positive and Gram-negative bacteria and also have antifungal and antiviral (adenovirus, papilloma virus, HIV and HSV) activity which derives from different modes of action including modulation of receptors on immunocompetent cells and inhibiting multiple steps of viral infectivity [44]. As with AMPs in general, the presumed mechanism of bacterial killing is binding of positively charged defensins to negatively charged bacterial membranes resulting in membrane permeabilization [44].

Cathelicidin

Cathelicidin peptides, including the human cathelicidin LL-37, mostly form an α-helical structure; cationic charge enables these AMPs to bind to negatively charged bacterial membranes [44]. In humans, only cathelicidin

LL-37 is expressed by neutrophils, mast cells and keratinocytes (after an inflammatory stimulus) as the major sources [6]. LL-37 shows a broad activity against Gram-positive and Gram-negative bacteria and works synergistically with other AMPs like β-defensins [58]. Besides its antimicrobial effect, LL-37 is able to chemoattract mast cells, neutrophils, monocytes and T cells to sites of inflammation and additionally modulates immune responses and re-epithelization of skin wounds [59], making LL-37 an interesting peptide for therapeutic intervention in infectious/inflammatory diseases [60].

Dermcidin

DCD was identified in the eccrine gland and appears to be the principal sweat AMP [61]. Other than defensins and cathelicidins, DCD is constitutively secreted in human sweat and is not inducible by injury and dermal inflammation [62]. Proteolytic cleavage of a 9.3-kDa precursor results in a peptide made of 47 amino acids (DCD-1) which – in low micromolar concentrations – shows antimicrobial activity against *S. aureus, Enterococcus faecalis, Escherichia coli* and *C. albicans* under in vitro conditions resembling human sweat [61]. Contrary to defensins and cathelicidins, DCD-1 most likely does not kill bacteria by permeabilizing their membranes as DCD-1 is an anionic peptide showing a flexible structure with α-helices and β-sheets, depending on the environmental conditions [63]. The amount of DCD-1 in human sweat, which is 1–10 µg/ml in healthy humans [61], appears to be reduced in patients with atopic dermatitis [43].

Other AMPs

Besides defensins, cathelicidins and DCD, human skin expresses other AMPs such as proteinase inhibitors, chemokines and neuronal proteins/peptides with RNase 7 and psoriasin (S100A7) as the most prominent representatives [44]. The highly basic 14.5-kDa protein RNase 7 [64] is one of the major heparin-binding proteins in healthy human stratum corneum [43]. In addition to its relative abundance in human skin, the expression of RNase 7 can further be induced by proinflammatory cytokines and possibly by bacteria [64, 65]. RNase 7 from human skin shows a broad activity against Gram-negative *(E. coli* and *P. aeruginosa)* and Gram-positive bacteria *(Propionibacterium acnes* and *S. aureus)* as well as against the yeast *C. albicans* [44]. In this sense, RNase 7 is one of the most potent and most efficacious human antimicrobial proteins known so far [43]. Recently, another member of the RNase family, RNase 8, has been identified as a novel AMP with broad-spectrum microbicidal activity [66].

Psoriasin is a calcium- and zinc-binding peptide that is expressed in healthy skin stratum corneum [44, 67] and in even higher amounts in psoriatic skin [68]. Psoriasin is the principal *E. coli*-bactericidal component and one of the innate barriers of healthy skin; *P. aeruginosa* and *S. aureus* are less susceptive [43, 44, 67].
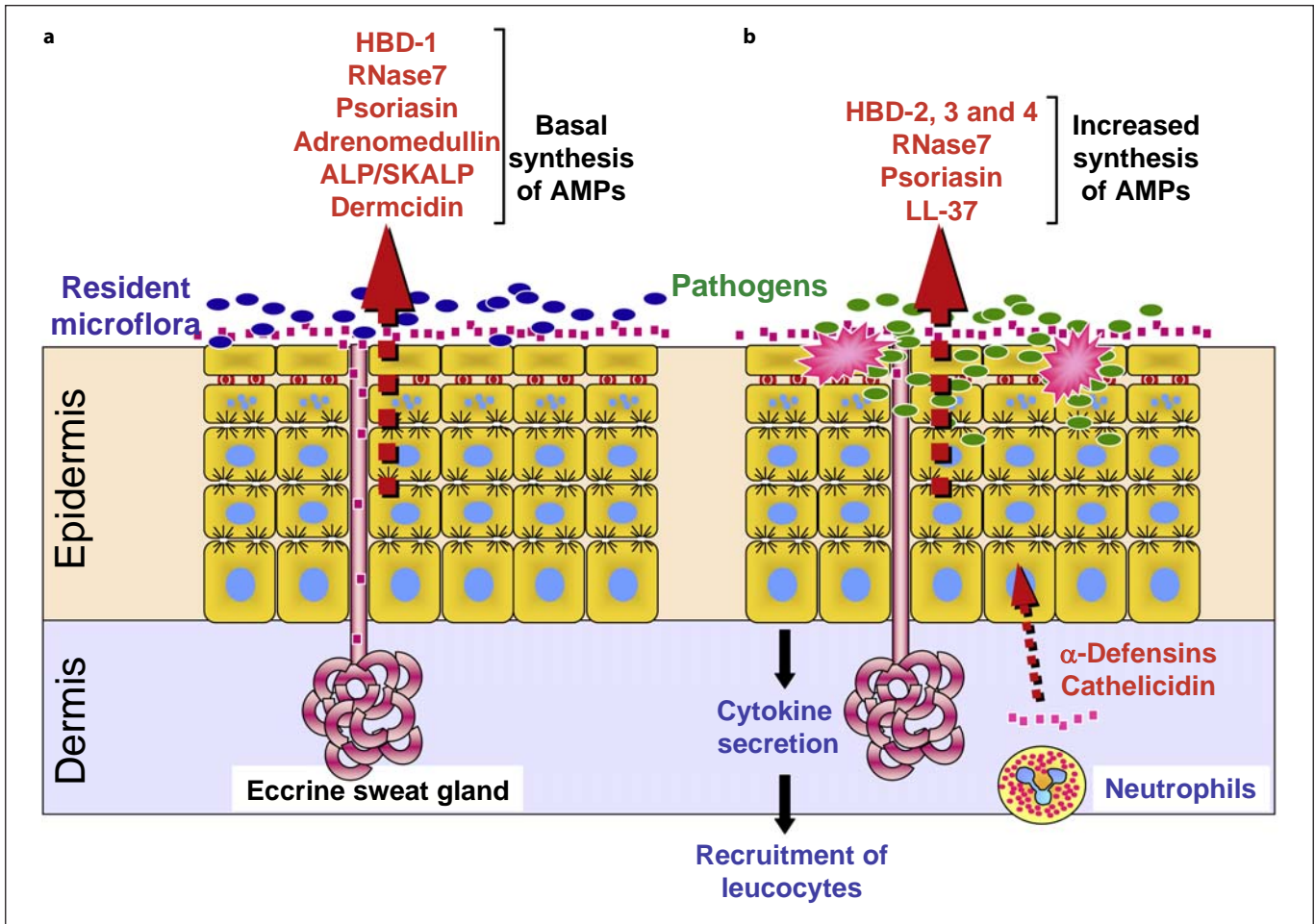
AMPs in Skin Diseases

What makes AMPs especially interesting for applied dermatology is the relation between the severity of various skin diseases and the expression of AMPs. Correlations can be positive or inverse [6, 44]. For example, there is an association between lowered levels of AMPs in burns as well as chronic wounds compared to normal skin. A reduced amount of DCD in the sweat coincides with an impaired innate defense of human skin, while AMP overexpression in human skin appears to be accompanied by an increased protection against infection in psoriasis, rosacea or in other inflammatory skin diseases [6]. These findings indicate that AMPs have a potential for therapeutic use. Before practical use, however, the role of a particular peptide in various skin diseases should be precisely known.

AMPs and Psoriasis

Psoriasis is an inflammatory non-infectious skin disease with typical inflammatory plaques reflecting hyperproliferation of the epidermis resulting in massive production of scale [6, 69]. Psoriasis is considered to be an autoimmune disease as in psoriatic lesions, high levels of proinflammatory cytokines, chemokines as well as activated T cells and antigen-presenting cells can be found. Interestingly, in the skin of patients with psoriasis, almost all known AMPs, such as the β-defensins HBD-2 and -3, the cathelicidin LL-37, psoriasin, RNase 7 as well as other AMPs (such as ALP/SLP1, Elafin/SKALP), are highly upregulated [6, 65] (see also fig. 3). The overexpression of AMPs accompanied by the synergistic interaction seems to be one major reason for the observed lowered susceptibility of psoriatic skin to cutaneous bacterial infections [70].

Although the mechanism of AMP induction in psoriatic skin is not completely understood, there seems to be a strong association with increased levels of cytokines like IL-1β and IL-6, as well as IFN-α and -γ [11, 71–74]. This hypothesis is supported by cathelicidin LL-37 induction of IFN-α [75].

Fig. 3. Illustration of the protective function of AMPs in normal skin (**a**) and infected and/or inflamed skin such as in psoriasis (**b**) (from Schittek et al. [6], with permission).

AMPs and Rosacea

Rosacea is a common chronic, often underdiagnosed, skin disease of uncertain etiology. The various clinical manifestations associated with this disease most frequently occur in the light-skinned Caucasian population, in persons between 30 and 50 years of age [76, 77]. The dermatological manifestations of rosacea mainly affect cheek, nose, chin, and central forehead. The earliest symptoms associated with rosacea are intermittent central facial flushing and erythema. Furthermore, the disease may be linked to ocular manifestations [78]. Until today, the pathogenesis of rosacea is not known in detail, yet evidence has been accumulating that rosacea with its common symptoms, such as inflammatory lesions, erythema, teleangiectasia, phy-

matous changes and ocular symptoms, is of inflammatory nature [79].

Most recently, it could be shown that symptoms of rosacea are exacerbated by factors that trigger innate immune responses, such as the release of cathelicidin AMPs produced by keratinocytes [80]. Clearly, there is a role of cathelicidin in skin inflammatory responses as individuals with rosacea express cathelicidin LL-37 at abnormally high levels in their facial skin, and specific proteolytically processed forms of cathelicidin peptides found in rosacea differ from those found in normal individuals [79, 81]. These forms, but not those from healthy skin, are able to induce the release of the proinflammatory IL-8 from keratinocytes [6]. This means that in the pathogenesis of rosacea, cathelicidin peptides likely are abnormal-

ly processed to forms that induce inflammation [7], providing evidence that the elevated levels of cathelicidins contribute to the chronic inflammatory reaction in the skin of patients with rosacea [6].

AMPs and Acne Vulgaris

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous units widely affecting adolescents and young adults. Characteristic of this skin disorder is the formation of comedones, papules, pustules, nodules and/or cysts as a result of obstruction and inflammation. The pathogenesis, as far as already known, involves excess sebum production, follicular hyperproliferation, inflammatory reactions and colonization with *P. acnes* [82]. In lesional and perilesional epithelium of patients with acne vulgaris, a marked upregulation of human β-defensins (HBD-1 and HBD-2) is found, in the case of HBD-2 most likely triggered by *P. acnes* and mediated by the Toll-like receptor (TLR) signaling pathway [83]. The role of other AMPs remains to be clarified, but it is known that β-defensins, cathelicidin LL-37 and psoriasin expressed in keratinocytes and sebocytes are able to kill *P. acnes* making these AMPs possible future candidates for therapeutic intervention oriented at the pathogenesis of acne. Another AMP interesting for the future treatment of acne is omiganan, a novel, synthetic, cationic analogue of the AMP indolicidin that was originally purified from the cytoplasmic granules of bovine neutrophils [84]. It demonstrates in vitro activity against a wide variety of microorganisms, including Gram-positive and Gram-negative bacteria and fungi [84]. Omiganan is the most advanced agent in the frontline of applications of AMPs [85] and is currently clinically tested for the treatment of acne and rosacea.

AMPs and Atopic Dermatitis

Atopic dermatitis is a complex chronic inflammatory skin disease which is characterized by xerosis, pruritus (itch) and erythematous lesions with increased transepidermal water loss [86]. Atopic dermatitis significantly affects the quality of life of patients and their families. New insights into the pathophysiology of the disease refer to an important role of structural abnormalities in the epidermis associated with immune dysregulation [87]. Typically, patients with atopic dermatitis show a predisposition to colonization or infection by various microorganisms, in particular *S. aureus* and HSV A [87]. Some studies analyzing AMPs in lesional skin show that, in contrast to psoriasis, rosacea and acne vulgaris, atopic dermatitis is characterized by less expression of AMPs, especially of cathelicidin LL-37 and HBD-2 [72, 88, 89]. It has been hypothesized that a reduced induction of AMPs in atopic dermatitis may contribute to the increased susceptibility of skin infections, in particular with *S. aureus* [72, 90]. However, most of the studies investigating AMP expression levels in atopic dermatitis skin have compared these levels primarily to those in psoriatic skin, not to healthy skin [72, 88, 89]. Gläser et al. [91] observed that the expression and secretion of psoriasin was more strongly induced in atopic dermatitis skin compared to healthy skin, indicating that AMP expression is not generally reduced in atopic dermatitis. An enhanced expression of RNase 7, psoriasin and HBD-2 and HBD-3 in atopic dermatitis lesional skin compared to non-lesional skin and healthy controls is possibly triggered by a disturbed skin barrier. Thus, the role of AMPs in atopic dermatitis, especially with regard to the control of *S. aureus* colonization, remains to be elucidated in more detail [92].

AMPs and Skin Injury/Wounds

The functional role of constitutively and inducibly expressed AMPs after skin injury and in chronic wounds also needs further analysis. At present, data from the literature suggest that AMPs, such as cathelicidin LL-37, HBD-2, HBD-3, psoriasin and RNase 7, are upregulated after skin injury, including burnt skin [5, 21, 44], whereas cathelicidin expression is low or even absent in the chronic wound stage [6, 44]. As LL-37 has a direct effect on wound healing by promoting neovascularization and angiogenesis [5, 93], this AMP seems to be the most promising agent for future therapeutic approaches in order to antagonize impaired wound healing.

AMPs and Other Skin Diseases

There are also other skin diseases with an altered AMP expression, but pertinent data are somewhat fragmentary and not completely consistent as yet. In general, inflammatory skin diseases seem to be associated with an increased expression of AMPs. For example, HBD-2 has been shown to be upregulated in superficial folliculitis [94] and HBD-1 to HBD-3 mRNA levels in localized scleroderma [95]. High expression of HPN-3 has been found in cutaneous T-cell lymphoma patients [96]. Condyloma acuminatum and verruca vulgaris are associated with an increase in cathelicidin LL-37 expression [97]. Altogether, the precise function of AMPs in the mentioned skin diseases, however, remains to be further clarified.

From Bench to Bedside: The Future

On the basis of the new insights into the cellular and molecular roles of AMPs in human skin and in certain skin diseases described above, it is to be expected that a second wave of new 'from bench to bedside' AMPs will contribute to our therapeutic armamentarium within a few years [23].

Several AMPs are currently undergoing laboratory testing and the application of these peptides in in vitro experiments and animal models is seemingly successful [45]. However, despite undeniable successes in the preclinical area, only few AMPs have reached the phase of testing in clinical trials so far [45, 98, 99]. At present, four AMPs were successful in therapeutic clinical trials [5]. Pexiganan, a derivative of magainin, which has been developed for the treatment of infected foot ulcers in patients with diabetes mellitus and which entered phase III trials [45] and has been shown to be equally effective as oral ofloxacin, was finally not approved by the US Food and Drug Administration [98]. Omiganan has completed one phase II study for the treatment of rosacea and two phase II studies for the treatment of acne, the latter demonstrating evidence of efficacy against all acne lesion types [100]. One possible reason for the fact that clinical studies and, even more so, the large phase III studies with AMPs are very rare is the still limited knowledge on stability of peptides, although stability problems can be largely overcome by adding protease inhibitors [45]. A possibly even more important reason that so few AMPs have been clinically tested up to now appears to be a possible cytotoxicity of AMPs [45, 101]. For example, the mammalian AMP protegerin-1 reduced the bacterial count in a murine sepsis model, yet it also reduced the survival rate – probably by inducing endotoxin release and, as a result, modifications in the host innate immune response [102].

Despite the problems of cytotoxicity of AMPs, in topical treatment of skin diseases, they are certainly less significant than in the systemic therapy of infectious and/or inflammatory diseases. However, it is important to mention in this regard that, although tyrothricin can only be administered topically because of its systemic toxicity, it is still effective *and* well tolerated in the therapy of skin disease. Recently, strategies have increasingly been devised aiming at a reduced cytotoxicity of AMPs and, if possible, at the same time at an improved antimicrobial activity [5].

One of these strategies is to make designer peptides such as P-novispirin G10 [103]. They exhibit low cytotoxic activity and often at the same time show an improved therapeutic efficacy, as it has been shown for a bactericidal immunomodulatory fusion peptide of HBD-3 with a mannose-binding lectin, even against MRSA [104]. Another promising strategy is to develop analogues or truncated molecules of human AMPs, e.g. of cathelicidin LL-37, being less hemolytic and toxic as well as more effective compared to native LL-37 [105, 106]. Finally, some scientists substitute several L-amino acids in AMPs to achieve a reduced toxicity [107] or combine conventional antibiotics with AMPs in order to ensure high antimicrobial activity and low toxicity [5, 108] while at the same time reducing the risk of bacterial resistance. Although it cannot as yet be said which of these strategies will ultimately succeed and will help to bring new AMPs or their derivatives to the clinic to treat infectious and/or inflammatory skin diseases, the fact remains that intensive work is being done on these issues worldwide.

Conclusion

Based on new insights into the cellular and molecular roles of AMPs in human skin and in infectious/inflammatory skin diseases, it is to be expected that AMPs or their recombinant analogues will contribute to our therapeutic armamentarium within a few years. Strategies have increasingly been devised aiming at a reduced cytotoxicity of AMPs and ideally at the same time at an improved antimicrobial activity. Nevertheless, presently 'old' AMPs, such as tyrothricin, are still of clinical importance in the treatment of infectious skin diseases and may experience a renaissance as natural antibiotics.

Disclosure Statement

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