

# Antimicrobial peptides

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Acids and barrier lipids of the stratum corneum (horny layer) are the skin's first line of defence against infections. However, they also are the basis for a typical microbial colonisation (skin flora). The skin flora contains harmless but also facultative pathogenic germs. Peptide structures neutralise these pathogenic but also exogenous germs when they attempt to penetrate into the skin.

The natural antimicrobial peptides (AMP) of the body are essential components of the epithelia, or in other words, the boundary tissues of multicellular animal and animal organisms. The epidermis and the mucous membranes of the eyes, nose, mouth cavity, gastrointestinal tract and the vagina as well as the epithelia of the urethra and the lungs appertain, among others, to the outward human epithelia.

## Broad-spectrum antibiotics

AMPs are particularly significant whenever epithelia are injured and become porous. In this case, the risk of infections is increased. The particularly versatile AMPs are activated by different mechanisms. In the case of infections, their synthesis is stimulated and additional AMPs are produced. Contrary to the immune system, AMPs attack the microorganisms in a non-specific way. This implies that the activity of AMPs can be compared with that of broad-spectrum antibiotics. AMPs can be activated, *inter alia*, via contact with metabolic products and enzymes of the germs (e.g. proteases). Flagellin, a globular protein occurring in the flagella of bacteria, is a typical trigger for the formation of psoriasin and defensins (AMPs of the skin).

Dermcidin (DCD), also an AMP, forms in the sweat glands and finds its way to the skin surface with the sweat. DCD fragments as for instance DCD-1L form ion channels in the membranes of bacteria with the consequence that the membrane potential is imploding. Zinc ions have synergistic effects in this context. People with atopic eczema who frequently suffer from infections show a comparably lower concentration of DCD-1L in their sweat.<sup>1</sup>

<sup>1</sup> Paulmann M, Arnold T, Linke D, Özdirekcan S, Kopp A, Gutschmann T, Kalbacher H, Wanke I, Schuenemann VJ, Habeck M, Bürck J, Ulrich AS, Schitteck B, Structure-activity analysis of the dermcidin-derived peptide DCD-1L, an anionic antimicrobial peptide present in human

## Modes of action

AMPs usually attack by dipping into the membranes of microorganisms with a cationic (positively charged) molecular residue. Hence, they are remotely related to the synthetic cationic preservatives as for instance chlorhexidine, polyaminopropyl biguanide (PHMB) and quats such as benzalkonium chloride. Besides its anionic, DCD-1L also has a cationic residue which is particularly active in the acidic environment of sweat. The cationic character of AMPs is due to the basic amino acids arginine, lysine and histidine. The effect of AMPs not only depends on their charge but also on the ratio of lipophilic and hydrophilic sections in their structures. Here again a parallel becomes apparent to the preservatives listed in the Cosmetic Directive: their partition coefficient between lipophilic and hydrophilic phase of a cream is crucial for the antimicrobial effect.

An essential characteristic of various AMPs is their ability to eliminate vital trace elements such as iron, manganese and zinc (see above) from the microorganisms. In this way they incapacitate their oxidoreductases which depend on the heavy metals and the germs die off.

Another mode of action may be the inhibition of bacterial proteases. Proteases are enzymes that serve microorganisms to solubilize and metabolize the proteins of their unintentional hosts. This allows them to penetrate their host. The efficacy of protease inhibitors against inflammatory processes can be observed in the context of skin care for instance when boswellic acids of frankincense resins<sup>2</sup> are used as

sweat, *The Journal of Biological Chemistry* 287 (11), 8434-8443 (2012)

<sup>2</sup> Tausch L, Henkel A, Siemoneit U, Poeckel D, Kather N, Franke L, Hofmann B, Schneider G, Angioni C, Geisslinger G, Skarke C, Holtmeier W, Beckhaus T, Karas M, Jauch J, Werz O, Identification of human cathepsin G as a functional target of boswellic acids from the anti-inflammatory remedy frankincense, *J Immunol* 183(5), 3433-3442 (2009)

exogenous active agents. They have anti-inflammatory effects in the case of acne, rosacea, perioral dermatitis and atopic skin prone to infections.

### Ample protection

Depending on their source and structure, AMPs have antibacterial, antifungal and antiviral effects or are effective against single-cell organisms. The following representatives are significant:

- **Psoriasisin:** The AMP occurs in the skin and specifically in psoriasis lesions. It is effective against *Escherichia coli* (intestinal bacteria) and stimulated by the flagellin of the bacteria.<sup>3</sup>
- **Calprotectin** is an AMP with high affinity to the trace elements manganese and zinc. It has antimicrobial effects due to the complexation of these elements. Calprotectin occurs in the granulocytes.
- **Defensins** occur on the skin and the mucous membranes. This type of AMPs primarily affects low cholesterol membranes of microorganisms and viruses<sup>4</sup>. Intestinal defensins are stimulated by probiotics.
- **Lysozymes** are ubiquitous in flora and fauna and belong to a large family of enzymes of the immune system that, besides other functions, primarily is effective against bacteria.
- **Cathelicidins** occur in epithelial cells. Their formation is endogenously stimulated. Chronic skin diseases such as atopic dermatitis, psoriasis and rosacea are characterized by a dysregulation of these antimicrobial peptides.<sup>5</sup> In the case of rosacea, the disorders are caused by cathelicidin-cleaving proteases. Facultative pathogenic bacteria benefit from this condition. The consequence is an increased presence of cathelicidin fragments in the skin.

<sup>3</sup> Schröder JM, Körpereigene Antibiotika schützen Haut und Schleimhaut, Pharmazeutische Zeitung 2010 (16) online

<sup>4</sup> Borkowski AW and Gallo RL, The coordinated Response of the Physical and Antimicrobial Peptide Barriers of the Skin, *J Invest Dermatol.* 2011;131(2):285–287

<sup>5</sup> Reinholz M, Ruzicka T, Schaubert J, Cathelicidin LL-37: an antimicrobial peptide with a role in inflammatory skin disease, *Ann Dermatol.* 2012;24(2):126-35

- **Dermcidin** is formed in the sweat glands.
- **Lactoferrin** contains iron, enzymatically inhibits various bacterial proteases and is found, among others, in milk and the vaginal secretion of mammals. The successful treatment of paradontitis with lactoferrin has been reported.<sup>6</sup> The enzyme is isolated from milk; it is a component of food supplements and cosmetics, but also naturally contained in milk-based products (mare's milk, breast milk etc.).
- **Ribonuclease-7** (RNase-7) is a highly effective AMP of the genitourinary tract<sup>7</sup> and the skin<sup>8</sup>.
- **Histatins** occur in the saliva of mammals. They contain the amino acid histidine as cationic acting component. Administration: gingivitis (histatin gel).<sup>9</sup>

### Nature as a model

Antimicrobial peptides are rather common in the fauna and their structures vary depending on the species. Plants also use AMPs in order to protect themselves against unwanted infections. In the case of lesions they release substances that trigger the synthesis of AMPs, among others. Unfortunately these substances cannot be used for the human skin. In other words, they are ineffective in this particular field. However, it is an elegant way of inducing the skin to produce endogenous peptidic antibiotics through external application of active agents. The molecules in question are comparably smaller than the AMPs that are pieced together of various amino acids. They are

<sup>6</sup> Berlutti F, Pilloni A, Pietropaoli M, Polimeni A und Valenti P, Lactoferrin and oral diseases: current status and perspective in periodontitis, *Ann Stomatol* 2011;2(3-4):10–18

<sup>7</sup> Spencer JD, Schwaderer AL, Wang H, Bartz J, Kline J, Eichler T, DeSouza KR, Sims-Lucas S, Baker P, Hains DS, Ribonuclease 7, an antimicrobial peptide upregulated during infection, contributes to microbial defense of the human urinary tract, *Kidney Int.* 2013;83(4):615-25

<sup>8</sup> Köten B, Simanski M, Gläser R, Podschun R, Schröder JM, et al. RNase 7 Contributes to the Cutaneous Defense against *Enterococcus faecium*, *PLoS ONE* 2009;4(7):e6424

<sup>9</sup> Paquette DW, Simpson DM, Friden P, Braman V, Williams RC, Safety and clinical effects of topical histatin gels in humans with experimental gingivitis, *J Clin Periodontol.* 2002;29(12):1051-8

easier to synthesize and administer and also more stable. This particular administration is comparable with the stimulation of endogenous growth factors by exogenously applied vitamin A or vitamin A acid. Although the first AMPs were discovered decades ago and various biochemical mechanisms have been known for a long time, appropriate developments still are at the very beginning.

In the meantime, a series of clinical studies on peptidic antibiotics have been conducted with native AMPs, synthetic AMP analogues and modified animal AMPs. They still have the disadvantage of a relatively complex composition, as already described above. Hence most of them could not gain acceptance – supposedly, this is due to the high production costs and inefficient routes of administration. However there is an exception to the rule, i.e. lactoferrin which occurs in milk. Observations on antimicrobial<sup>10</sup> and antiviral effects (warts<sup>11</sup>, herpes) of the peptide containing mucus of different snail species also are important in this context. These reports are in line with the indications found in European folk medicine.

### Skin care

What does that mean for skin care? The so far known physiological processes linked to the natural AMPs of the body show the significance of an intact skin for the prevention of infections. Accordingly, the skin care should also be as physiological as possible in order to generate synergies instead of counterproductive effects. A glance on the list of ingredients of cosmetics and treatments reveals that this is not common practice, though.

- Excess skin cleansing not only favours dehydrated skin but also involves the inactivation and wash out of the natural AMPs of the body. Consequently, the body is more susceptible to bacterial and fungal infections (mycoses).<sup>12</sup> This applies above all for the application of emulsifier and tenside containing preparations such as shampoos or

shower gels. Pure, soft water frequently is the better choice.

- Analogously, also excess intimate care in particular and excess care of mucous membranes in general is a potential factor for serious disorders in these areas which consequently lead to new infections.<sup>13</sup>
- Strong complexing agents that increase the oxidation stability of cosmetics, such as for instance EDTA, bind the trace elements iron, zinc, copper and manganese that are essential for the function of AMPs.<sup>14</sup>
- Years of fruit acid peelings increase the susceptibility of the skin to perioral dermatitis and rosacea; anaerobic bacteria are a significant factor in both cases.
- Uncritical use of antioxidants<sup>15</sup> also might influence the sensitive balance of AMPs.

AMPs are a fascinating skin care topic of the future. Let's be prepared for surprising results!

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<sup>10</sup> Zhong J, Wang W, Yang X, Yan X, Liu R, A novel cysteine-rich antimicrobial peptide from the mucus of the snail of *Achatina fulica*, *Peptides*. 2013 (39):1-5.

<sup>11</sup> Thomas S, Medicinal use of terrestrial molluscs (slugs and snails) with particular reference to their role in the treatment of wounds and other skin lesions, [www.worldwidewounds.com/2013/July/Thomas/slug-steve-thomas.html](http://www.worldwidewounds.com/2013/July/Thomas/slug-steve-thomas.html), Update July 2013

<sup>12</sup> Lautenschläger H, Die Barriere schützen – Hautpflege bei Pilzinfektionen, *medical Beauty Forum* 2013 (4), 48-50

<sup>13</sup> Lautenschläger H, Die Facetten der Intimpflege – Weniger ist mehr, *medical Beauty Forum* 2014 (2), 35-37

<sup>14</sup> Lautenschläger H, Spurenelemente – Kleine Lebenshelfer, *Kosmetische Praxis* 2011 (3), 13-15

<sup>15</sup> Lautenschläger H, Antioxidantien und Radikalfänger – zu viel ist zu viel, *Ästhetische Dermatologie (mdm)* 2015 (8), 12-16