Antimicrobial Peptides in Healthy Skin and Atopic Dermatitis

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ABSTRACT
Antimicrobial Peptides and Proteins (AMPs) represent effector molecules of the innate defense system in all organisms. AMPs are either constitutively or inducibly produced mainly by various epithelial cells, including keratinocytes. This report reviews our current knowledge about the major yet known keratinocyte-derived AMPs, its role in healthy skin and atopic dermatitis.

KEY WORDS
antimicrobial peptides, atopic dermatitis, defensin, innate immunity

INTRODUCTION
All multicellular organisms, including plants, invertebrates, vertebrates and humans, are in contact with potentially pathogenic microbes and are covered with an organism- and location-specific microflora, but are rarely infected. The human body contains nearly $10^{14}$ cells, of which only 10% are body cells; the remaining are microbes within the body (mainly in the gut) and at epithelial surfaces such as the skin and the upper aero-digestive tract as well as the genito-urinary tract.

Thus it is really surprising that these microbes do not infect the organisms, although there are several locations which might represent ideal habitats for microbes (such as the mouth, the genito-urinary tract, the gut and axillae) due to the presence of humidity, nutrients and electrolytes.

Effector cells of our immune system cannot explain this surprising fact because the by far majority of multicellular organism lack an immune system. Therefore it is tempting to speculate that there exists a very efficient, ancient defense system at body surfaces which protects the organisms from infection.

INNATE EPITHELIAL DEFENSE MECHANISMS IN PLANTS AND INVERTEBRATES

The roots of germinating plant seed are in contact with numerous soil bacteria and fungi, but remain uninfected. This is achieved by epithelial production and release of antimicrobial components, mainly peptides. These are mainly located within the upper-most epidermal cell layers of different plant organs.

Similarly invertebrates such as insects have a very effective epithelial defense system: Upon microbial challenge e.g. the fruit fly Drosophila melanogaster produces in a microbe-selective manner epithelial AMPs, which are highly active against the challenging microbe.

Unlike insects, which also contain a phagocyte-based defense system, the sweet water polyp Hydra vulgaris solely contains epithelial cells to defend infection. Indeed, the outer epithelia produce a number of AMPs, which at least in part are induced upon challenge of these animals with microbial products via a two-component “Toll-like-receptor-like Receptor”. This animal is living in ponds, being exposed to huge numbers of microbes such as Pseudomonas species, but not infected!

EPITHELIAL DEFENSE IN VERTEBRATES

The first evidence that also vertebrates possess an epithelial defense system comes from the observation that freshly operated frogs, which have been taken into a pond, usually did not develop wound infections. It was hypothesized that antimicrobial components, secreted from frog skin, protect wounds from infection. A subsequent analysis led to the discovery of the AMP Magainin.

Also mammalian epithelia are normally free of infection. In cattle a number of epithelia-derived AMPs called β-defensins have been identified, which show a more or less epithelia-specific expression pattern.
Most of these β-defensins are absent in healthy epithelia and are inducible upon contact with microbes.\(^7\) Apart from β-defensins, gut epithelia of mice are capable to produce structurally related α-defensins like the cryptdins\(^8\) and cryptdin-related peptides (CRPs)\(^9\) together with “cathelicidin-related antimicrobial peptides, CRAMPs”, which are also important for protection of skin infection.\(^{10}\) A role of at least some of these AMPs in the composition of the mouse gut flora as well as innate defence in the mouse gut is well documented.\(^{11}\)

**ANTIMICROBIAL PEPTIDES IN HUMAN EPITHELIA**

The findings that mammalian epithelia are capable to defend infection by production of β-defensins suggested that also human epithelial cells produce AMPs. In the gut, epithelial granulocytes (“Paneth cells”) represent a major source of antimicrobial peptides, in particular the α-defensin HD-5,\(^{12}\) which is a broad-spectrum antibiotic. Impaired HD-5 expression in the gut, as seen in Crohn’s disease,\(^{13}\) has been discussed as cause of recurrent infections and inflammation in the gut. Although HD-5 is also present in the genito-urinary tract, the anticyanobacterial peptide cathelicidin LL37 seems to represent its principle peptide antibiotic protecting the urinary tract against invasive bacterial infection.\(^{14}\)

In the lung\(^{15}\) again epithelial LL37 seems to be of relevance for innate defense, although a number of other AMPs—including the β-defensin-1 (hBD-1) seem to be relevant.\(^{16}\)

**INNATE ANTIBACTERIAL DEFENSE IN HEALTHY SKIN**

Healthy human skin is always covered with microorganisms, but usually not infected by them. For long time this per se unexpected observation was explained by the existence of a “physical defense shield” consisting in the stratum corneum and a layer of various lipids, together with an acidic pH.\(^{17}\) These parameters are really very important for maintaining an efficient protection, however is it sufficient?

Many microbes are known to optimally grow at acidic conditions or on lipids! Thus one would expect that human skin represents an optimal habitat for such bacteria—which is indeed the case. However why are these microbes unable to infect the skin under healthy conditions, despite the fact that sufficient nutrients seem to be there?

Because leukocytes are absent in healthy skin, the only convincing explanation would be the existence of an immune cell-independent keratinocyte-based skin defense system.

Thus, one would expect strategies of the skin to prevent infection without recruitment of inflammatory cells. This would implicate the existence of a “Chemical” or “Antimicrobial Defense Shield” of the skin, where location-dependent different effector systems are activated.\(^{18}\) The skin surface would use a strategy, which allows control of the microflora and prevent infection by pathogens by limiting its growth and/or its colonization.

Recent analyses support this hypothesis: Based on the observation that exposure of *E. coli* to the skin surface killed it, the principal surface-located factor was identified as psoriasisin (S100A7).\(^{19}\) Psoriasin is a preferentially *E. coli* killing AMP with a minimal inhibitory concentration (MIC) at low micromolar doses by sequestrating Zn\(^{2+}\), as revealed by sensitivity of psoriasin *E. coli*-cidal activity towards pretreatment with Zn\(^{2+}\).\(^{19}\) *In vitro* bactericidal concentrations are easily achieved at various skin areas as revealed by an *in vivo*-inhibition of bactericidal activity with a neutralizing antibody.

Immunohistochemistry revealed a focal S100A7-expression in the stratum granulosum and SC, the epidermis of the upper parts of hair follicles with strongest staining as well as in sebocytes and sebum.\(^{19}\)

Washing experiments indicated that psoriasin is secreted *in vivo* in a topospecific manner.\(^{19}\) Highest local amounts were detected in skin areas known to show highest bacterial loads, e.g. on palma, planta, axillae and the scalp.

In contrast to *E. coli*, the exposure of *Staphylococcus aureus* to skin does not kill them.\(^{20}\) This is in accordance with the fact, that skin washing fluid has a low *S. a.* killing capacity (unpublished results). Indeed, *S. a.* killing activity is rather located within the SC. As principal staphylocidal factor of SC-extracts RNase-7 (R7) has been identified.\(^{21}\) R7 is a broad-spectrum antimicrobial protein with strong activity at low micromolar concentration against various gram-positive and grammnegative bacteria as well as the yeast *Candida albicans*. Of particular interest is the unusual sensitivity of *Enterococcus faecium* and *E. faecalis* towards R7, which are killed at nanomolar concentrations.\(^{22}\)

R7 is constitutively produced by keratinocytes and can be induced further upon stimulation with interferon γ.\(^{21}\)

In contrast to skin washing fluid, SC-extracts revealed strong staphylocidal activity, which could be markedly blocked by neutralizing R7-antibodies, a finding which supports an important role of R7 in natural defense against *S. a.* skin infection.\(^{23}\) This is further supported by *ex vivo*-experiments with skin explants, where R7-antibody pretreatment of skin explants led to an increased *S. a.* growth.\(^{23}\)

Thus, the stratum corneum itself may act, apart from its physical barrier properties, as a second “Chemical Defense Shield”, which contains several antimicrobial peptides and proteins.

Using a biochemical approach in heel SC extracts as second principal *S. aureus* killing AMP lysozyme...
has been identified. It should be noted that, unlike in secretions such as saliva, tears or vaginal secretions, skin washing fluid does not contain lysozyme, suggesting that lysozyme in healthy skin is rather a component of the "second chemical barrier", located within the corneocytes. Interestingly, most S. a. strains are resistant against lysozyme.

The third staphylocidal AMP of potential relevance in healthy skin and mucosa is calprotectin, a heterodimeric non-covalent complex of S100A8 and S100A9: Calprotectin represents one of the principal neutrophil proteins. It has been abundantly found in vaginal secretions and was recently identified to be focally expressed in different skin areas as well as mucosal epithelial cells. Calprotectin is a Ca²⁺-binding protein, which also can bind Zn²⁺ and Mn²⁺. Whereas Zn²⁺-binding properties account for its Candida-cidal activity, Mn²⁺-binding properties cause S. aureus-killing properties.

Another AMP of potential relevance in healthy skin is Dermcidin, which represents the principle sweat antimicrobial peptide. Dermcidin is constitutively produced exclusively by eccrine gland cells. It is expressed as a 9.5 kDa-precursor, which, after proteolytic cleavage, forms dermcidin 1 (DCD-1), a 47-aa-peptide fragment with antimicrobial activity against S. aureus and other bacteria and fungi at concentrations in the range 1-10 μg/ml. Anionic as well as cationic dermcidin-peptides reveal similar antimicrobial properties without showing visible membrane effects upon ultrastructural analyses. It is therefore likely that dermcidin has yet not known intracellular targets in S. aureus.

### INNATE ANTIBACTERIAL DEFENSE IN INFLAMED SKIN

Upon skin infection several AMPs are induced in keratinocytes. The quantitatively most abundant inducible AMP is human beta-defensin-2 (hBD-2). It is absent in healthy skin, but found as one of the quantitatively dominating peptides in lesional psoriatic skin. hBD-2 can be induced by proinflammatory cytokines such as IL-1α, IL-1β, TNF-α as well as IL-17 and IL-22.

IL-17 and IL-22 seem to be the most powerful hBD-2-inducers in primary keratinocyte cultures in vitro. hBD-2 is focally expressed in lesional keratinocytes of the stratum granulosum e.g. in psoriasis lesions and wounds or in infected skin areas. Papillomavirus-infection also seems to induce hBD-2, which may point towards a yet unproven possible role of hBD-2 as a papillomavirus-infection targeting factor.

hBD-2 is targeting grammegative bacteria-such as E. coli und Pseudomonas aeruginosa and to a lesser extent also yeasts-such as Candida albicans. It is almost inactive against S. aureus, suggesting that this defensin might play a limited role as antibiotic in epithelial defense responses against S. aureus. hBD-2 can also be induced by bacterial pathogen-associated molecular patterns, FAMPs.

Although several studies have shown that in epithelial cells of the lung and the skin stimulation with bacterial lipopolysaccharide (LPS)-preparations lead to a transcriptional hBD-2-induction, concentrations of the stimulus were in the range of 1-100 μg/ml, suggesting that likely a trace contamination accounts for the hBD-2-induction. Indeed, the use of chemically synthesized LPS did not induce hBD-2 (our unpublished results). TLR2-ligands have been controversially discussed to be inducers of hBD-2. Whereas it was shown that TLR2 and NALP2 mediate induction of hBD-2 by Fusobacterium nucleatum in gingival epithelial cells, in primary skin keratinocytes a synthetic TLR2 ligand did not induce hBD-2.

The as yet most potent and efficient inducer of hBD-2 (transcription and protein production) is the TLR5-ligand flagellin, which is active at picomolar concentrations.

Interestingly, flagellin is present as a soluble protein after shedding from Pseudomonas aeruginosa, when these bacteria are colonizing and forming biofilms, which occurs at starvation conditions. The shedding is mediated by rhamnolipids, a special kind of biosurfactants generated upon quorum sensing.

hBD-2 is also efficiently induced in skin keratinocytes by the synthetic TLR3-ligand PolyI: C, which may indicate that the natural TLR3-ligand double stranded RNA represents an important hBD-2 inducer. The observation that also TLR9 ligands induce a moderate hBD-2-induction in keratinocytes let also microbial DNA be able to activate the hBD-2 production in keratinocytes.

Another important inducible epithelial AMP is hBD-3. This AMP is mostly absent from healthy skin, but it is strongly induced in psoriasis lesions, upon wounding as well as in infection. hBD-3 is, unlike hBD-2, a broad-spectrum peptide antibiotic. It is active against S. aureus, various Gram-negative bacteria as well as Candida albicans at low micromolar concentrations. Ultrastructural analyses of hBD-3-treated S. aureus reveal blebs and cell wall disruption, similar as seen for Penicillin-treated S. a. Recent studies have shown that hBD-3 inhibits cell wall biosynthesis in S. a. by interference with the lipid II biosynthesis, similar as seen for the fungal defensin plectasin.

Tissue studies of hBD-3 expression revealed transcripts in epithelia of many organs and in some non-epithelial tissues. As major sources of hBD-3 keratinocytes of the skin and gingiva, trachea, esophagus, tonsils, placenta, heart, skeletal muscle and fetal thymus were identified.
High amounts of hBD-3 peptide are found in keratinocytes of the wound edge and in lesional psoriatic skin.

Whereas IL-1 is one of the most powerful hBD-2-inducers, IFNγ is the most potent and efficient hBD-3-inducing cytokine. Although the direct contact of epithelial cells with bacteria lead to hBD-3-induction in vitro and in vivo, followed by bacterial killing, the mechanism needs to be elucidated, although most likely it is mediated by an EGFR-ligand. The most powerful hBD-3-inducers are EGFR-ligands such as TGF-α and other, at the keratinocyte surface located ligands of the EGFR. Therefore a transactivation process, which is mediated by metalloproteinase-dependent shedding of cell-bound EGFR-ligands, seems to be the most relevant pathway of hBD-3-induction in vivo.

The cathelicidin LL37 is another inducible AMP. It is produced as a precursor termed hCAP18, which is cleaved by proteases to generate antimicrobially active C-terminal fragments like LL37. Neutrophils represent the by far dominating cellular source of hCAP18, where it is located in the secondary (“specific”) granules. Proteinase 3 cleaves hCAP18 generating the cathelin domain and the antimicrobial peptide LL37. hCAP18 is expressed by many cells including lung epithelial cells and skin keratinocytes. Keratinocytes express hCAP18/LL37 at sites of inflammation. In skin, hCAP18 is processed by KLK5, resulting in multiple C-terminal cleavage products. The in vivo concentration of keratinocyte-derived LL37 in skin seems to be too low to exert direct antimicrobial effects. But several immunomodulatory properties of LL37 have been identified, which indicate that this peptide is rather acting as a host-defense peptide than as an AMP. Indeed, LL37, after binding to DNA, acts as ligand for TLR9 and activates plasmacytoid dendritic cells for IFN-α production.

Mature LL37 peptide has been found in sweat, although another study failed to detect it using SELDI-TOF-MS.

Mechanisms of hCAP18/LL37-induction in skin are not well understood. hCAP18/LL37 immunoreactivity is found in keratinocytes at the wound edge and after treatment with Vitamin D3 [1,25(OH)2D3], as seen in macrophages.

It should be notified, however, that hCAP18/LL37-immunoreactivity was mainly seen in the basal keratinocyte layer, unlike the defensins, RNase-7 and psoriasin, thus supporting the hypothesis that hCAP18/LL37 has a different function in skin innate defense.

**ANTIMICROBIAL PEPTIDES AND ATOPIC DERMATITIS**

Patients with atopic dermatitis (AD) often suffer from bacterial and viral infections of the skin. Among bacterial infections *S. aureus* is the predominant pathogen. Nearly 90% of AD patients have been shown to be colonized with *S. aureus*, whereas only 5 to 30% were colonized in a control population.

These observations forced the hypothesis that an impaired epidermal AMP-expression in atopic skin may contribute to an increased susceptibility towards *S. a.*-infection.

Indeed, when the expression of hBD-2 and LL-37 in the epidermis of AD patients and patients with psoriasis was compared, a markedly reduced expression of both AMPs was seen. However with these findings it was difficult to explain the increased *S. a.* infections in AD patients, because hBD-2 is preferentially killing Gram-negative bacteria and the role of keratinocyte-derived LL-37 in defense of *S. a.*-infection is not clear. With the hypothesis that possibly an epidermis-derived, *S. a.*-killing AMP is of importance, the expression of hBD-3 has been investigated. By immunohistochemistry and realtime PCR epidermal expression of hBD-3 was seen to be much lower in AD, when compared with psoriasis lesions. It was hypothesized that Th2-cytokines like IL-4 and IL-13 may cause this low expression, because both inhibited the expression of hBD-2 and hBD-3 in keratinocyte cultures. This observation is of particular importance because hBD-3 has been identified as an important keratinocyte-derived AMP that is able to control the growth of *S. aureus* in a skin explant model.

The role of hCAP18/LL-37 in atopic skin remains elusive. Recent studies have shown that healthy skin and non-lesional atopic and psoriatic skin show very low hCAP18/LL-37 level. Although the previous finding of decreased levels of hCAP18/LL-37 mRNA and hCAP18/LL-37-immunoreactivity in lesional atopic skin (compared with lesional psoriatic skin) was confirmed, there are marked differences in the immunohistochemistry data: Whereas Ballardini et al. found increased hCAP18/LL-37-immunoreactivity in epidermal cells close to injury as well as in dermal infiltrate cells, Mallbris et al. reported about decreased immunostaining in keratinocytes close to injury in atopic dermatitis. Reasons for these discrepancies are yet not clear, but may originate from the use of a monoclonal vs polyclonal hCAP18/LL-37 antibody.

Nevertheless, there seem to be differences, when the role of barrier disruption was studied: A very recent study indicated that in AD lesions, in contrast to healthy persons, the expression of hCAP18 mRNA was markedly suppressed following wounding.

Investigations on the role of Dermcidin (DCD), which is constitutively expressed in human eccrine sweat glands and secreted into sweat, have shown that patients with AD have a reduced amount of DCD peptides in sweat. Moreover, the amount of several DCD-derived peptides, which are at least in part potent staphylocidal peptides, in sweat of patients with AD were found to be reduced. Interestingly, in AD...
patients with a history of bacterial and viral skin infections less DCD-1 peptides were found in their sweat. In healthy subjects, sweating was observed to lead to a reduction of viable bacteria on the skin surface, but this was not seen in patients with AD. Thus, DCD peptides in sweat of patients with AD may contribute to the high susceptibility of these patients to skin infections and altered skin colonization, although its role in *S. aureus* colonization of healthy skin remains to be determined.

In a recent systematic analysis, putatively relevant AMPs (constitutively produced RNase 7 and psoriasin, and the inducible AMPs, hBD-2 and hBD-3) were determined in healthy, psoriatic, and chronic as well as acute atopic skin. Tissues samples and skin washing fluids derived from healthy and SCORAD- and *S. aureus* colonization-matched AD-patients were analyzed for the expression and the *in vivo* secretion of these AMPs. As a result the authors have shown that all four AMPs are induced in both non-lesional and lesional skin of psoriatic and atopic patients when compared with the skin of healthy individuals.

It was further found that superficial barrier disruption by tape stripping, which caused in healthy skin an increased production and release of psoriasin, also induced the expression of hBD-2, hBD-3, and RNase 7. Thus the enhanced expression of AMPs in psoriatic and AD skin may be driven—at least in part—by a disrupted epidermal barrier.

The absolute levels of AMP expression and secretion were found to be lower than levels detected in psoriasis, which is in agreement with published results, but in this study neither a correlation between the secretion of AMPs (RNase 7, psoriasin, hBD-2, and hBD-3) and *S. aureus* colonization nor a correlation between AMP secretion and SCORAD was found. These findings may be interpreted that reduced amounts of the analyzed AMPs, in particular the most abundant staphylocidal AMPs of healthy skin, do not cause the increased susceptibility of AD skin to *S. aureus* colonization and infection.

**ATOPIC DERMATITIS AND REGULATION OF EPITHELIAL ANTIMICROBIAL PEPTIDE PRODUCTION**

Several previous studies reported about decreased tissue expression of various skin-AMPs in AD-patients, when compared with patients with psoriasis, which suggest that induction and regulation of keratinocyte-derived AMP production and release is altered in AD, relative to psoriasis. A recent study, however, revealed no significant differences in the differences of the expression-levels in lesional skin vs non-lesional skin of the AMPs cathelicidin, hBD-2 and hBD-3 in AD, relative to psoriasis. However, a history of eczema herpeticum is associated with the inability to induce these AMPs in the skin of AD patients. A critical inducer of AMPs upon infection is IL-17A, which often acts synergistically with IL-22. These cytokines represent the most powerful inducers of keratinocyte-derived AMPs such as hBD-2, S100A7, S100A8/A9. On the other side, IL-17 has been shown to be essential for host defense against many microbes, particularly extracellular bacteria and fungi.

This is further supported in the autosomal dominant hyper-IgE syndrome (HIES, ‘Job’s syndrome’), which is characterized by recurrent and often severe pulmonary infections, eczema, staphylococcal abscesses and mucocutaneous candidiasis. Here mutations presumed to underlie HIES have recently been identified in the gene encoding STAT3 (signal transducer and activator of transcription 3). STAT3 signaling is essential for the generation of Th17 cells and the inability to produce Th17 cells is a mechanism underlying the susceptibility to the recurrent infections commonly seen in HIES. Further, the finding that IL-17A (-/-) mice show an increased susceptibility to infection by *S. aureus*, a direct relationship seems to be intriguing.

Therefore a lack of major AMP inducers such as IL-17 in AD skin, and suppression of AMP induction by elevated levels of Th2 cytokines, demonstrated *in vitro* for IL-4, IL-10, and IL-13, would explain the lower AMP levels in AD when compared with psoriasis. Interestingly, a recent study revealed that in patients with acute exacerbation of AD, secretion level of hBD-2 and RNase 7 were higher when compared with patients with chronic AD. In addition, hBD-3 has been detected in the lesional skin of 80% of the patients characterized by acute exacerbation of AD. Increased Th2 cytokine level, which have been associated with acute AD, appear not to be sufficient enough to inhibit the induction of AMPs, such as hBD-2, hBD-3 and RNase 7, in the acute AD lesion.

The data of this study further indicate that the induction of AMPs is not generally impaired in the skin of patients suffering from AD.

Nevertheless, the role of Th17 cells and IL-17A in AD is still elusive: In contrast to what has been expected, increased IL-17+ T cells have been identified in tissue sections of acute AD lesions relative to normal skin. Another study also demonstrated increased IL-17 expression in chronic AD lesions, when compared with normal skin, but the overall expression of the IL-23/TH17 pathway is much reduced compared with psoriasis.

Among the known principal staphylocidal keratinocyte-derived AMPs, only S100A8/A9 is induced by IL-17/IL-22. There is yet no experimental evidence that hBD-3 (which is induced in these cells by IFN-γ and EGFR-ligands) and RNase-7 (which is constitutively expressed and further induced by yet unknown mechanisms upon inflammation) are induced by IL-17.

More strikingly, there has been found a strong cor-
relation between RNase 7 transcript number, but not for hBD-2 or hBD-3, in healthy skin and the propensity of healthy individuals to develop S. aureus-positive skin infections. This is in accordance with the finding that R7 protein is the most relevant staphylolidal AMP in SC-extracts. Therefore R7 could represent a candidate AMP in AD-associated S. aureus infection. Although in a recent study no decreased RNase-7 amounts were detected in AD-skin-washing fluids, the concentrations were far below bactericidal concentrations. It is possible that amounts of SC-bound R7 differ between AD-patients and healthy persons.

CONCLUSION AND OUTLOOK

Although there is lots of evidence that keratinocyte-derived AMPs have an important role in controlling microbial growth and inhibiting infection at the surface of healthy skin, it is still not clear, why recurrent S. aureus skin infections occur in AD. An important factor promoting skin infection in AD is a disturbed skin barrier. The barrier defect leads to an increased microbial growth and inhibiting infection at the wound margin. But this seems—not to be the case. All yet available experimental data point towards a role of keratinocyte-derived AMPs rather at a quantitative than qualitative level.

It is currently not clear whether we are missing key components controlling S. aureus infection at the AD skin surface: One important and yet not well addressed problem could be the role of the commensal microflora in controlling skin-infection. Microbes can produce AMPs (so-called microcins), which are more or less target-microbe-specific. So, if the microflora on AD skin is altered, this would have effects on colonization of S. aureus—as seen in healthy persons. Further, the commensal microflora—as all bacteria—is able to produce low molecular antibiotics, which have neither studied at the skin surface nor in detail in all components of the human skin microbiom.

Future studies will address key questions on the role of low MW antibiotics, which have been secreted in situ by the residential microflora—together with surface-located host epithelia-derived AMPs and its precursors.

Studying these complex processes will enable us to better understand the initial phases of bacterial skin infection in AD and especially to get a convincing explanation, why especially S. aureus causes skin infection in AD.

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