Received: 16 April 2022 | Revised: 19 April 2022 | Accepted: 21 April 2022

DOI: 10.1002/ctm2.865

CLINICAL AND TRANSLATIONAL MEDICINE Open Access WILEY

COMMENTARY

Targeting the cutaneous microbiota in atopic dermatitis: 'A new hope' or 'attack of the CoNS'?

Chia-Yu Chu

Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

Correspondence
Chia-Yu Chu, Department of Dermatology, National Taiwan University Hospital, 7 Chung-Shan South Rd., Taipei 10002, Taiwan.
Email: chiayu@ntu.edu.tw

Funding information
Ministry of Science and Technology of Taiwan, Grant/Award Number: MOST 109-2314-B-002-052-MY3

Abstract

Although evidence showing that *Staphylococcus aureus (S. aureus)* is directly causative of atopic dermatitis (AD) is still lacking, there is evidence that *S. aureus* abundance is associated with disease flares and therapeutic responses. Patients receiving ATx201 OINTMENT 2% twice-daily had a significant reduction in the abundance of *S. aureus* and increasing Shannon diversity of skin microbiome compared to vehicle after seven days. A small molecule with a narrow-spectrum effect, especially on *S. aureus*, might be an attractive alternative for the treatment of AD.

KEYWORDS
AD, biofilm, microbiome, *Staphylococcus aureus*, *Staphylococcus epidermidis*

Atopic dermatitis (AD) is a disease characterised by itchy and inflamed skin frequently associated with skin infections and has been clearly shown to have an altered skin bacterial flora when compared to non-AD subjects.[1] A recent meta-analysis reported the prevalence of *Staphylococcus aureus (S. aureus)* carriage by patients with AD was 70% on lesional skin compared with 39% on non-lesional skin of the same patients or skin of healthy controls.[2,3] The rate of *S. aureus* colonisation was related to disease severity.[3]

Although evidence showing that *S. aureus* is directly causative of AD is still lacking, there is evidence that *S. aureus* abundance is associated with disease flares and therapeutic responses,[4] and *S. aureus* colonisation can drive AD-like disease in mice.[5]

Coagulase-negative staphylococci (CoNS) are a heterogeneous group of nearly 40 species that compose the majority of the Staphylococcus genus.[6] Some CoNS species are able to fight against pathogens. Several previously unknown and potent anti-*S. aureus* molecules have been discovered to be produced by skin CoNS species, such as *S. epidermidis*, *S. hominis* and *S. lugdunensis*.[2,7] The antimicrobial activity was identified as antimicrobial peptides (AMPs) produced by CoNS species including *S. epidermidis* and *S. hominis*. These AMPs were strain-specific, highly potent and synergised with the human AMP LL-37 that could selectively kill *S. aureus*.[1] Some recent studies also suggest that topical application of commensal organisms such as *S. hominis* or *Roseomonas mucosa* could reduce AD severity, which supports an important role for commensals in decreasing *S. aureus* colonisation in patients with AD.[2] Another study also showed that the human commensal *S. caprae* may compete with *S. aureus* by inhibiting quorum sensing. Through signal interference, *S. caprae* reduces methicillin-resistant *S. aureus* burden in both skin colonisation and infection.[6]

In this issue of Clin Transl Med, Weiss et al.[8] investigated the potency and the spectrum of ATx201 (niclosamide) in pre-clinical models and further analysed its propensity for resistance evolution. The impact of ATx201 OINTMENT

2% on the skin microbiome and load of *S. aureus* was then assessed in a clinical trial in patients with mild-to-severe AD. They found that ATx201 has a narrow distribution of minimal inhibitory concentration (0.125–0.5 μg/ml) consistent with its mode of action – targeting the proton motive force effectively stopping cell growth. In a Phase II trial of 36 patients with mild-to-severe AD, they showed that patients receiving ATx201 OINTMENT 2% twice daily had a significant reduction in the abundance of *S. aureus* and increasing Shannon diversity of skin microbiome compared to vehicle after 7 days.[8] However, the impact of ATx201 on the healthy skin microbiota and specificity of ATx201's effect to *S. aureus* remains to be fully elucidated. Accordingly, higher-resolution metagenomics and longer treatment duration such as 28, 42 or 84 days are still needed along with approaches to quantitate whether increases in Shannon diversity result primarily from a reduction in *S. aureus* or a regrowth of the commensal microbiota. Furthermore, direct evidence of clinically significant improvement is still lacking.

Microbiome therapies are emerging therapies with the objective to reduce the abundance of *S. aureus* and increase microbial diversity by introducing one or more beneficial commensal strains. It was reported that transplantation of *S. hominis* and *S. epidermidis* strains reduced the bacterial load of *S. aureus* on the skin of AD patients, through exerting antimicrobial activity towards *S. aureus*.[1] The presence of Esp-secreting *S. epidermidis* was also shown to eliminate the nasal colonisation of *S. aureus* by diminishing the biofilm formation of *S. aureus*.[9] While therapies based on addition of living bacteria represent a promising therapeutic approach, it remains unclear whether the use of transplants of specific commensal bacteria can eliminate resistant strains on the human AD skin. Long-term stability of using commensal microorganism is another concern.[8]

S. epidermidis has commonly been regarded as a beneficial skin microbe to against *S. aureus*. However, a recent study[10] found that the overabundance of *S. epidermidis* on some atopic patients can act similarly to *S. aureus*. Some strains of *S. epidermidis* may cause skin barrier damage and inflammation through secretion of the cysteine protease EcpA, and that this correlated with human disease severity.[10] These findings suggest that *S. epidermidis* may shift from a beneficial commensal to a deleterious pathogen similar to *S. aureus* in the permissive growth conditions of AD skin. Some unique CoNS strains, such as *S. hominis* A9 and C5, are able to inhibit the *S. epidermidis* accessory gene regulator (agr) quorum sensing system and thus prevent *S. epidermidis*-induced skin damage.[10] *S. hominis* A9 has been shown to have the capacity to kill *S. aureus*, whereas *S. hominis* C5 synthetic autoinducing peptide was shown to inhibit the *S. aureus* agr system.[10] Therefore, such commensal CoNS strains might be potential therapeutic tools to reduce *S. aureus* colonisation and both *S. aureus* and *S. epidermidis* toxin production in AD. The above findings indicate the complexity of the interactions between commensal CoNS and deleterious *S. aureus* and suggest that using *S. epidermidis* as the treatment for dysbiosis in AD may further damage the skin and cause inflammation. Thus, a small molecule with a narrow-spectrum effect, especially on *S. aureus*, might be an attractive alternative for the treatment of AD.

ACKNOWLEDGEMENTS

This work was supported by a grant from the Ministry of Science and Technology of Taiwan (MOST 109-2314-B-002-052-MY3).

CONFLICT OF INTEREST

None.

ORCID

Chia-Yu Chu https://orcid.org/0000-0002-9370-3279

REFERENCES

1. Nakatsuji T, Chen TH, Narala S, et al. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. *Sci Transl Med*. 2017;9:eaah4680. https://doi.org/10.1126/scitranslmed.aah4680
2. Paller AS, Kong HH, Seed P, et al. The microbiome in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2019;143:26-35. https://doi.org/10.1016/j.jaci.2018.11.015
3. Totté JE, van der Feltz WT, Hennekam M, et al. Prevalence and odds of *Staphylococcus aureus* carriage in atopic dermatitis: a systematic review and meta-analysis. *Br J Dermatol*. 2016;175:687-695. https://doi.org/10.1111/bjd.14566
4. Kong HH, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res*. 2012;22:850-859. https://doi.org/10.1101/gr.131029.111
5. Kobayashi T, Glatz M, Horiuchi K, et al. Dysbiosis and *Staphylococcus aureus* colonization drives inflammation in atopic dermatitis. *Immunity*. 2015;42:756-766. https://doi.org/10.1016/j.immuni.2015.03.014
6. Paharik AE, Parlet CP, Chung N, et al. Coagulase-negative Staphylococcal strain prevents *Staphylococcus aureus* colonization and skin infection by blocking quorum sensing. *Cell Host Microbe*. 2017;22:746-756e5. https://doi.org/10.1016/j.chom.2017.11.001
7. Zipperer A, Konnerth MC, Laux C, et al. Human commensals producing a novel antibiotic impair pathogen colonization. *Nature*. 2016;535:511-516. https://doi.org/10.1038/nature18634
8. Weiss A, Delavenne E, Matias C, et al. Topical niclosamide (ATx201) reduces *Staphylococcus aureus* colonization and increases Shannon diversity of the skin microbiome in atopic dermatitis patients in a randomized, double-blind, placebo-controlled phase 2 trial. *Clin Transl Med*. 2022.
9. Iwase T, Uehara Y, Shinji H, et al. *Staphylococcus epidermidis* Esp inhibits *Staphylococcus aureus* biofilm formation and nasal

colonization. *Nature*. 2010;465:346-349. https://doi.org/10.1038/nature09074

10. Cau L, Williams MR, Butcher AM, et al. *Staphylococcus epidermidis* protease EcpA can be a deleterious component of the skin microbiome in atopic dermatitis. *J Allergy Clin Immunol*. 2021;147:955-966. https://doi.org/10.1016/j.jaci.2020.06.024

How to cite this article: Chu C-Y. Targeting the cutaneous microbiota in atopic dermatitis: 'A new hope' or 'attack of the CoNS'? *Clin Transl Med*. 2022;12:e865. https://doi.org/10.1002/ctm2.865