The Crosstalk Between Skin Microenvironment and Skin Microbiota in Atopic Dermatitis

Xu Yao

Hospital for Skin Disease, Chinese Academy of Medical Sciences

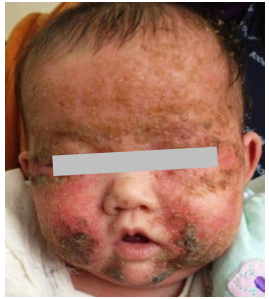
Email: dryao_xu@126.com

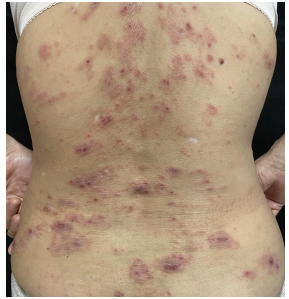
Conflict of Interest

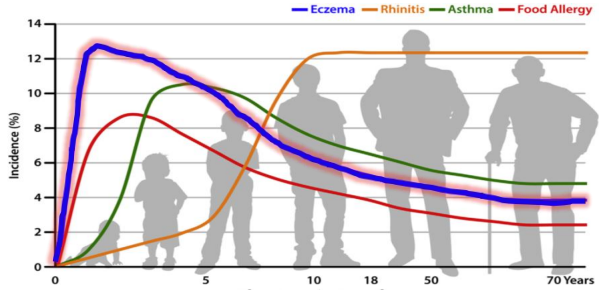
- I have a collaborative relationship with 01 Life Technology.

Atopic Dermatitis, (AD)

- A common, chronic and inflammatory skin disease.
- Gained global comprehensive attention.







atopic march

High prevalence

- The prevalence rate is **20%** among children and **5%** in adults

heavy burden

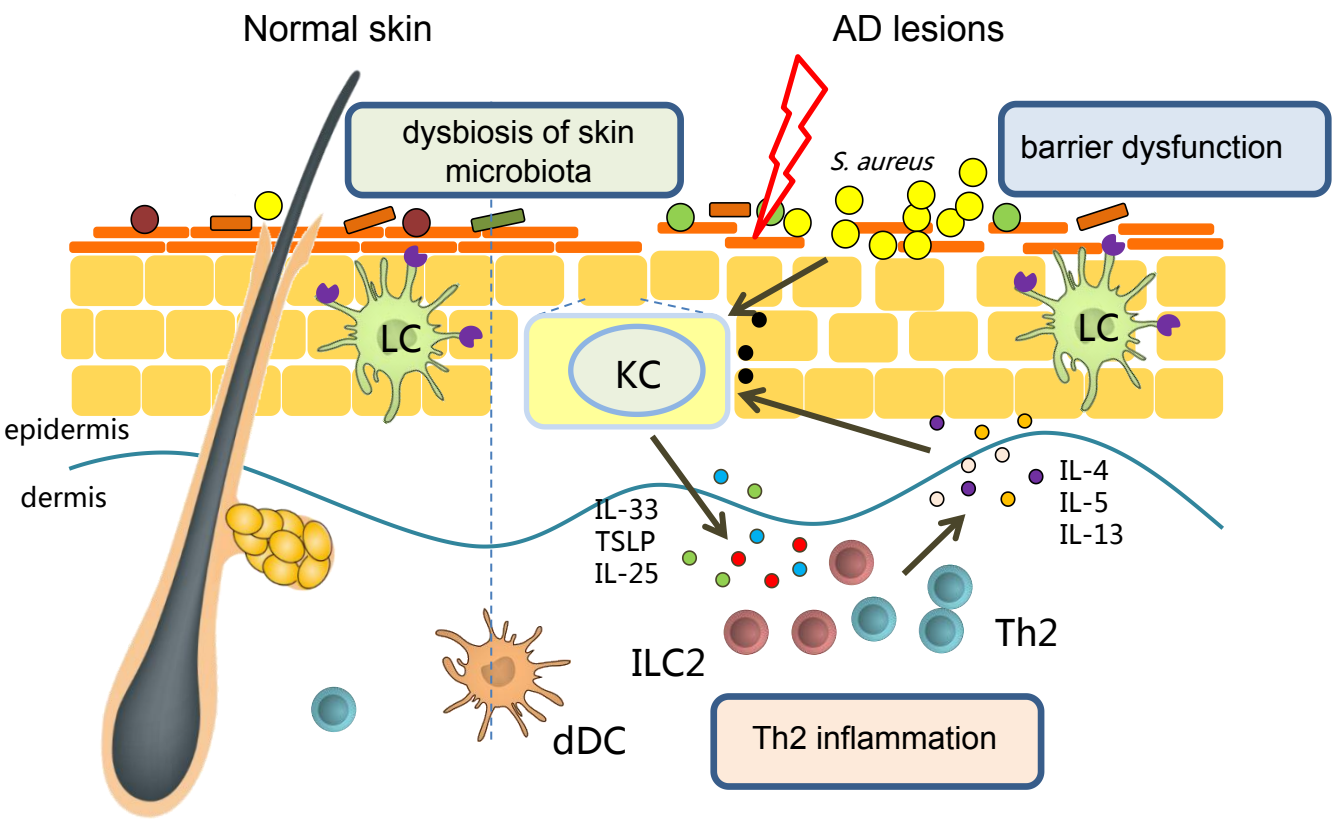
- Intractable pruritus and refractory dermatitis
- With **the highest disease burden** among all non-fatal skin conditions

Multi morbidities

- The **onset of allergy march**
- Frequently associated with comorbid allergic, metabolic, and neurosychiatric disorders.

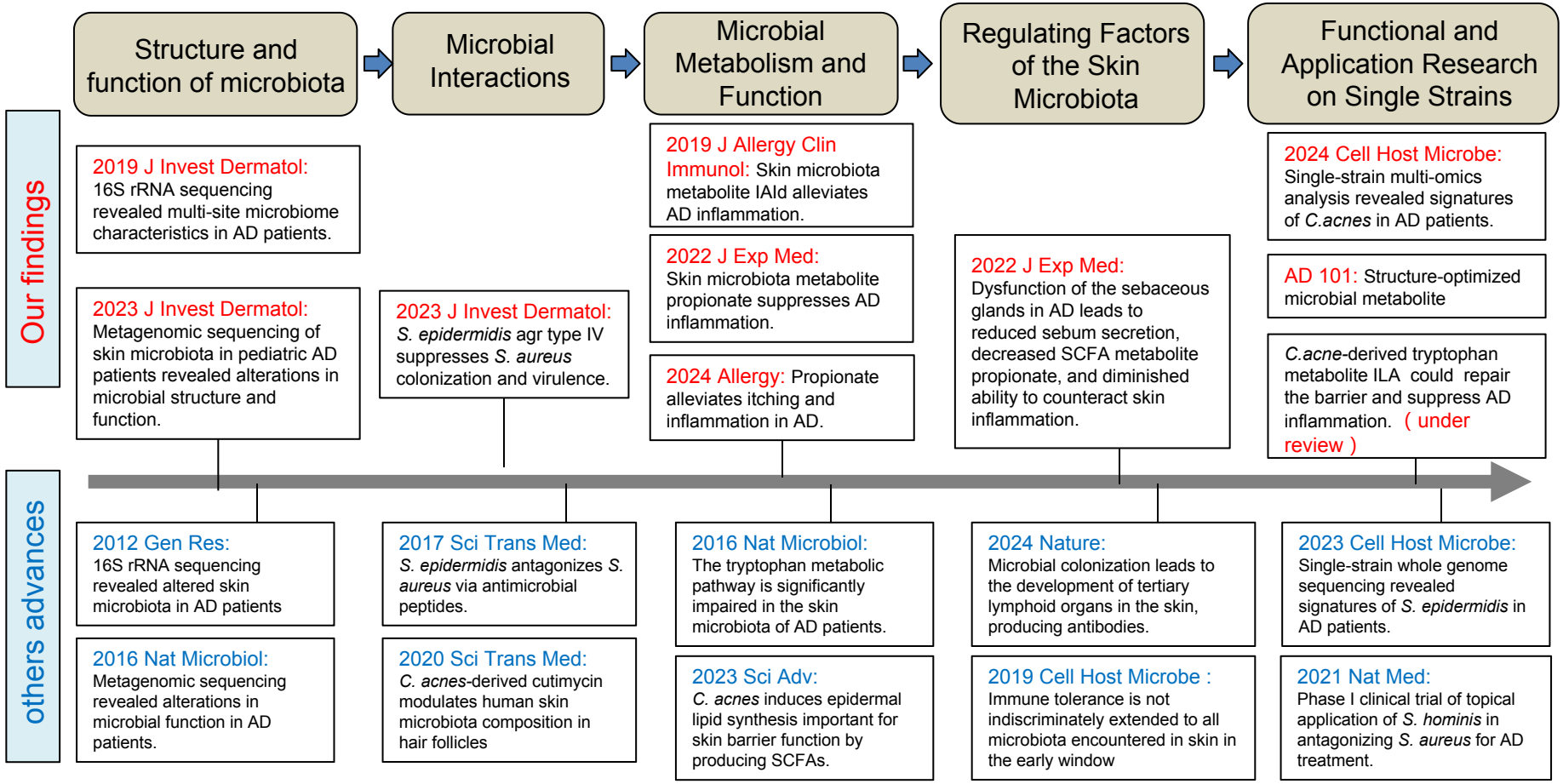
Lancet. 2025
J Clin Med. 2023

The Pathogenesis of AD

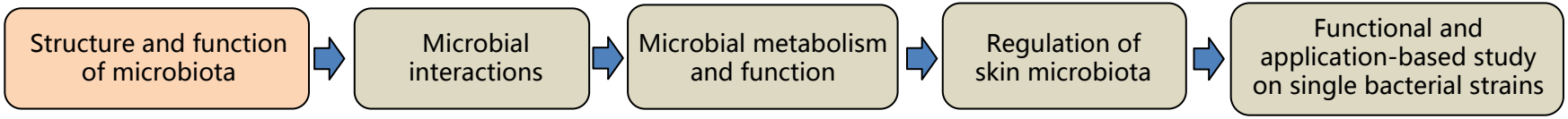


Adapted from Li W, Yosipovitch G. *Am J Clin Dermatol* 2020.

Advancing Researches on the Skin Microbiome of AD



Advancing Researches on the Skin Microbiome of AD



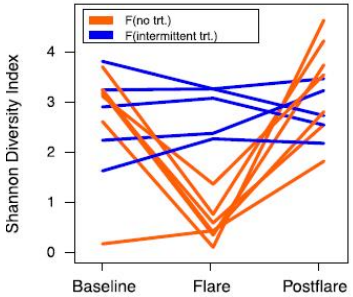
*** The articles marked in red are the research works of our team**

Alteration in the Skin Microbiota of AD—Disease Severity

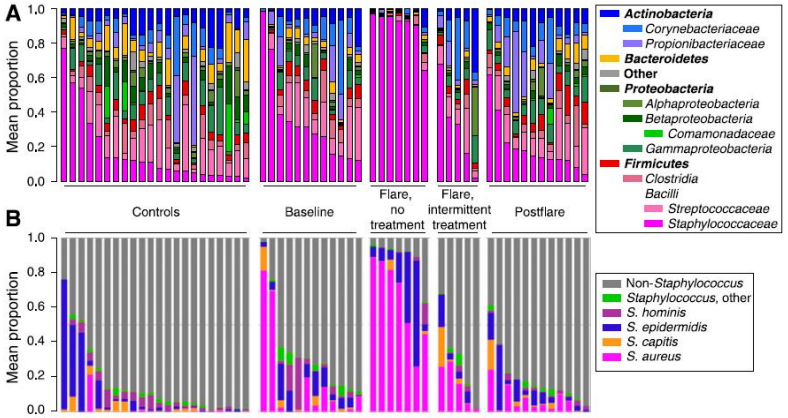
Research

Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis

Heidi H. Kong,[1,8] Julia Oh,[2] Clay Deming,[2] Sean Conlan,[2] Elizabeth A. Grice,[2] Melony A. Beatson,[1] Effie Nomicos,[1] Eric C. Polley,[3] Hirsh D. Komarow,[4] NISC Comparative Sequence Program,[5,7] Patrick R. Murray,[6] Maria L. Turner,[1] and Julia A. Segre[2,8]



- In AD patients, microbial disturbances are most significant in the acute phase and tend to be resolved during remission.
- The reduced diversity of skin microbiota is negatively related with disease severity;
- The increased abundance of *S. aureus* is positvely correalted with disease severity;



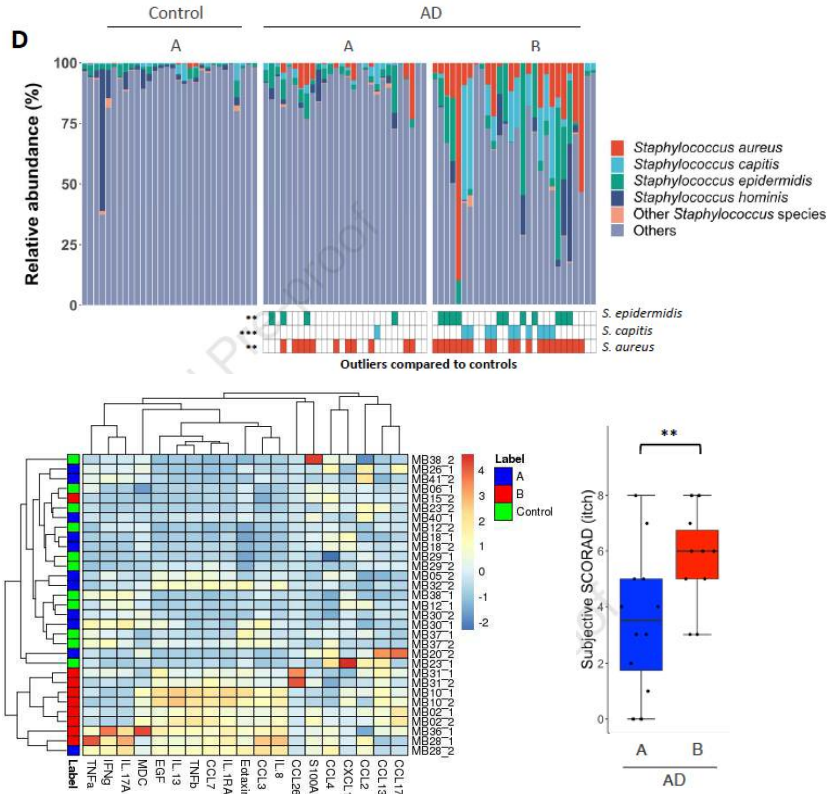
Kong et al. Genome Res. 2012; 22: 850–859.

Alteration in the Skin Microbiota of AD—Disease Subtypes

Atopic dermatitis and inflammatory skin disease

Atopic dermatitis microbiomes stratify into ecologic dermotypes enabling microbial virulence and disease severity

Angeline S. L. Tay, PhD,[a]* Chenhao Li, PhD,[b]* Tannistha Nandi, PhD,[b]* Kern Rei Chng, PhD,[b] Anand Kumar Andiappan, PhD,[c] Vijaya Saradhi Mettu, PhD,[d] Camille de Cevins, MSc,[b] Aarthi Ravikrishnan, PhD,[b] Charles-Antoine Dutertre, PhD,[c] X. F. Colin C. Wong, MSc,[a] Amanda Hui Qi Ng, BSc,[b] Sri Anusha Matta, PhD,[e] Florent Ginhoux, PhD,[a,c] Olaf Rötzschke, PhD,[c] Fook Tim Chew, PhD,[e] Mark B. Y. Tang, MD,[f,g] Yik Weng Yew, MD,[f] Niranjan Nagarajan, PhD,[b,h] and John E. A. Common, PhD[a] *Singapore*



- The skin microbiota of AD patients can be classified into two types: Type A and Type B.
- Type A: milder dermatitis and a microbial composition similar to that of healthy individuals.
- Type B: more severe dermatitis, characterized by reduced abundance of *Cutibacterium*, *Peptococcus*, and *Methylobacterium,* along with increased abundance of *Staphylococcus*.

Angeline S L. Tay, et al. J Allergy Clin Immunol, 2020

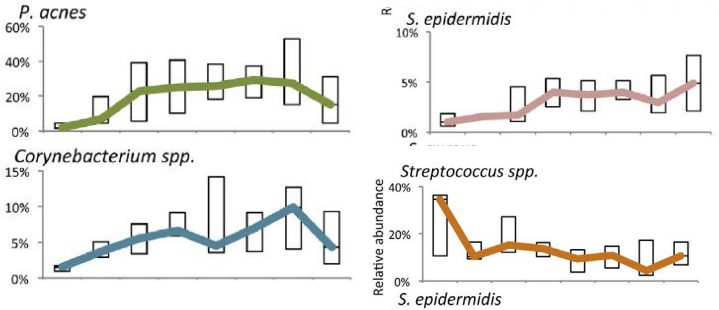
Alteration in the Skin Microbiota of AD—Age related

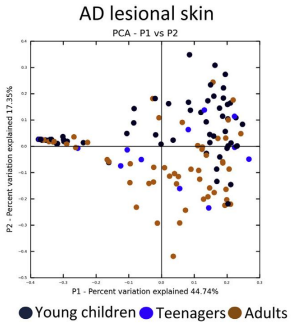
The skin microbiome is different in pediatric versus adult atopic dermatitis

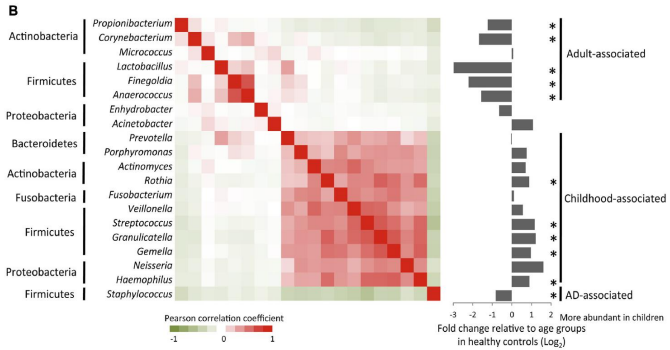
To the Editor:

Donald Y. M. Leung, MD, PhD[c,e]
Huiying Li, PhD[a,f]

- The composition of the skin microbiota in healthy individuals shifts with age.
- The abundance of *P. acnes* increases with age, while that of *Streptococcus* declines.







- In AD patients, the skin microbiota also undergoes age-related changes, forming distinct clusters compared to those of healthy children and adults.

Shi et al. J Allergy Clin Immunol. 2016; 138: 1233-1236

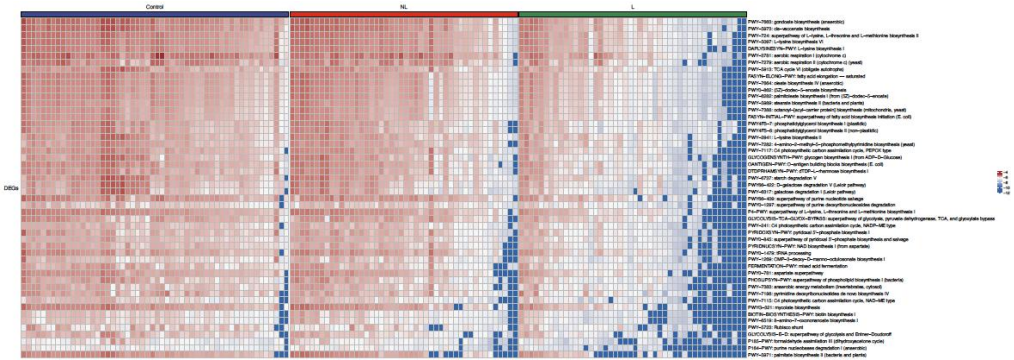
Metagenomics Charateristics of the skin microbiota in Children with AD

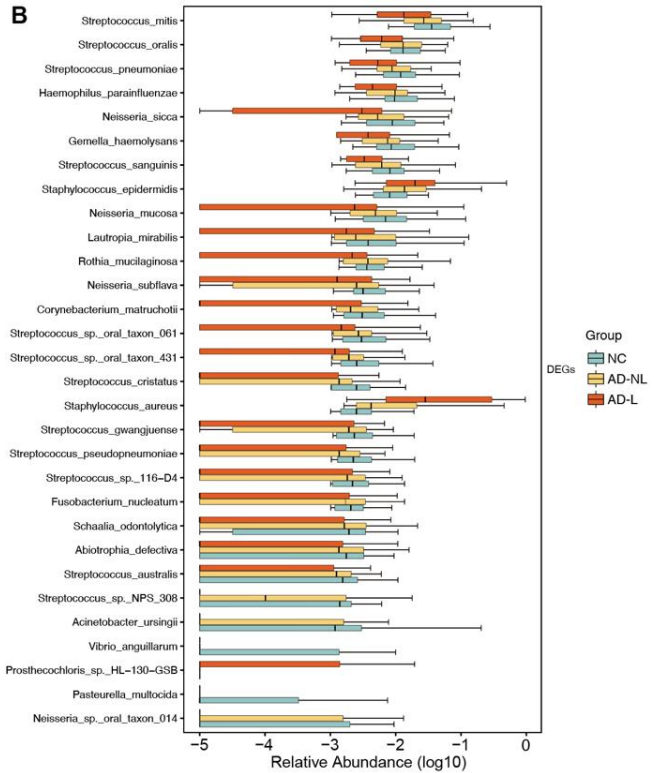
ORIGINAL ARTICLE

Heterogeneous Regulation of *Staphylococcus Aureus* by Different *Staphylococcus Epidermidis agr* Types in Atopic Dermatitis

Yuan Zhou[1], Xiaoqiang Xu[2], Yang Liu[3], Ao Wang[1], Yang Luo[1], Xiaochun Liu[1], Xiaokai Wang[4], Wei Li[2] and Xu Yao[1]

- A significant reduction in the alpha diversity of the skin microbiota, with a more pronounced decrease in lesional skin
- Multiple metabolic pathways were downregulated in lesional skin compared to non-lesional skin.





Zhou Y, et al. Journal of Investigative Dermatology (2023) 143, 2484-2493

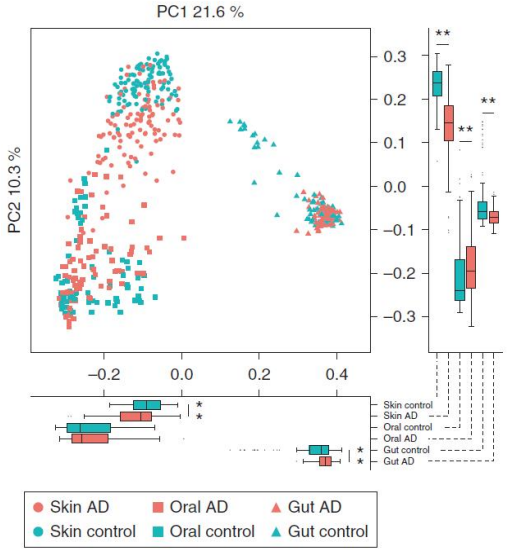
Alteration in the Skin Microbiota of AD—Comparison of multiple sites

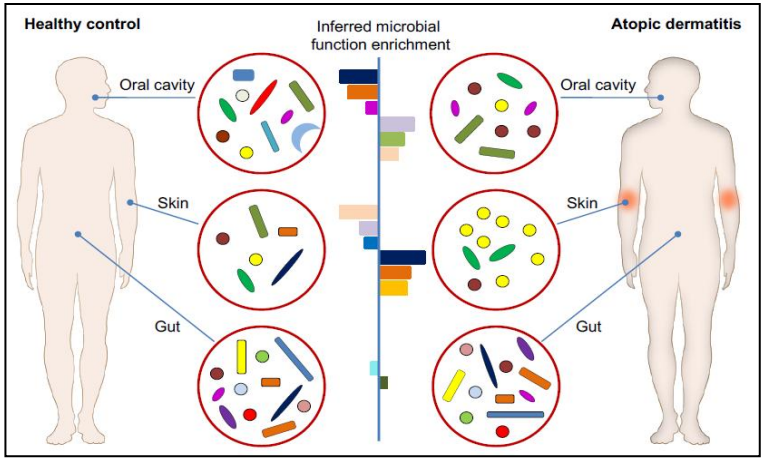
ORIGINAL ARTICLE

Inverse Association Between the Skin and Oral Microbiota in Atopic Dermatitis

Wei Li[1,2,6], Xiaoqiang Xu[3,6], He Wen[1,6], Zhifeng Wang[3,6], Chao Ding[4,5], Xiaochun Liu[1], Yingxia Gao[1], Huichun Su[1], Jingxi Zhang[1], Yue Han[1], Yan Xia[3], Xiaokai Wang[3], Heng Gu[1] and Xu Yao[1]

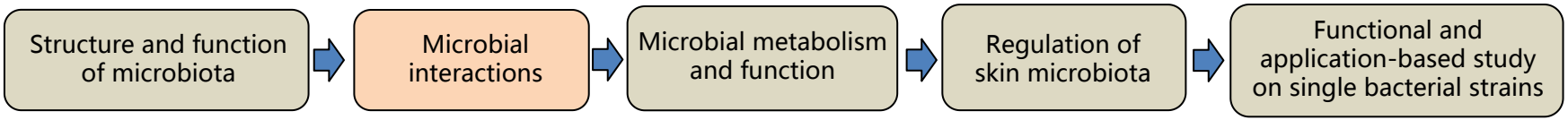
- The skin, oral and gut microbiota of AD exhibit varying degrees of association with the disease
- The skin and oral microbiota show an inverse correlation in AD patients.





Li et al. J Invest Dermatol. 2019 ;139:1779-1787.

Advancing Researches on the Skin Microbiome of AD



*** The articles marked in red are the research works of our team**

Antimicrobial peptides produced by skin commensals antagonize *S. Aureus*

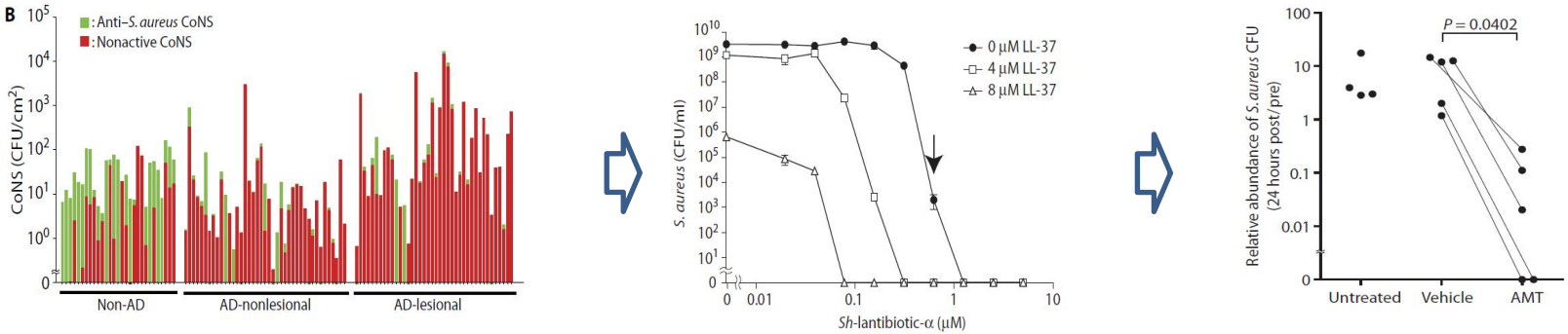
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

MICROBIOME

Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis

Teruaki Nakatsuji,[1] Tiffany H. Chen,[1] Saisindhu Narala,[1] Kimberly A. Chun,[1] Aimee M. Two,[1] Tong Yun,[1] Faiza Shafiq,[1] Paul F. Kotol,[1] Amina Bouslimani,[2] Alexey V. Melnik,[2] Haythem Latif,[3] Ji-Nu Kim,[3] Alexandre Lockhart,[4] Keli Artis,[4] Gloria David,[4] Patricia Taylor,[5] Joanne Streib,[5] Pieter C. Dorrestein,[2,6] Alex Grier,[7] Steven R. Gill,[7] Karsten Zengler,[3] Tissa R. Hata,[1] Donald Y. M. Leung,[5] Richard L. Gallo[1]*

- Coagulase-negative *staphylococci* (CoNS) with anti-*S. aureus* activity are less frequently detected in AD patients than in HCs.
- These CoNS produce antimicrobial peptides that act synergistically with LL-37 to inhibit *S. aureus*



Nakatsuji et al. Sci Transl Med. 2017;9, eaah4680

The quorum sensing system mediates microbial interactions involved in AD inflammation

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

MICROBIOME

Quorum sensing between bacterial species on the skin protects against epidermal injury in atopic dermatitis

- *S. aureus* disrupts the skin barrier and mediates inflammation by producing PSMα.
- Coagulase-negative *staphylococci* produce AIP, which inhibits the Agr system of *S. aureus*, thereby suppressing PSMα expression.

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

ATOPIC DERMATITIS

***Staphylococcus* Agr virulence is critical for epidermal colonization and associates with atopic dermatitis development**

- *S. aureus* on the skin of AD children has a fully functional Agr system, promoting bacterial colonization and virulence.
- The Agr system of *S. aureus* on the skin of healthy children is impaired.

Williams *et al*. *Sci. Transl. Med. 2019;* **11**, eaat8329
Nakamura *et al*. *Sci. Transl. Med. 2020;* **12**, eaay4068

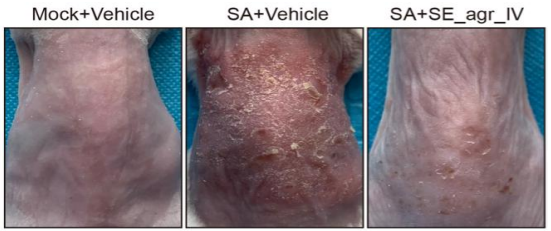
Agr type IV *S. epidermis* attenuates AD inflammation by inhibiting *S. aureus*

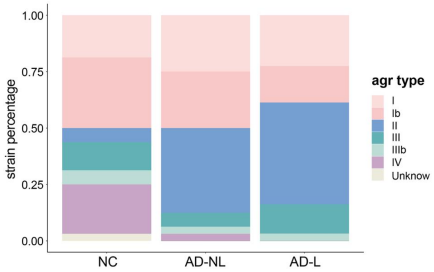
ORIGINAL ARTICLE

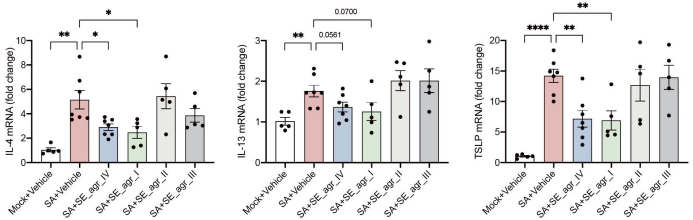
Heterogeneous Regulation of *Staphylococcus Aureus* by Different *Staphylococcus Epidermidis agr* Types in Atopic Dermatitis

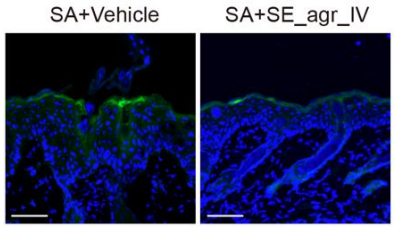
Yuan Zhou[1], Xiaoqiang Xu[2], Yang Liu[3], Ao Wang[1], Yang Luo[1], Xiaochun Liu[1], Xiaokai Wang[4], Wei Li[2] and Xu Yao[1]

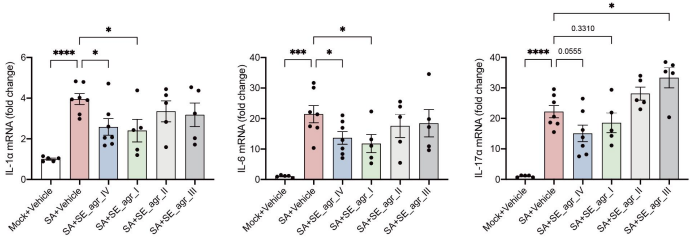
- The proportions of agr type IV and type I *S. epidermis* are decreased in AD patients.
- Agr type IV *S. epidermis* effectively inhibits the colonization of *S. aureus* and alleviates *S. aureus*-induced AD-like skin inflammation.





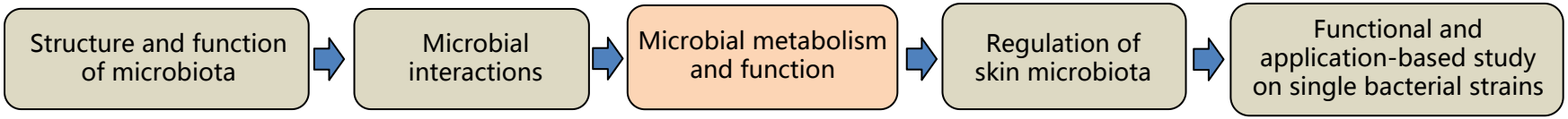






Zhou Y, et al. Journal of Investigative Dermatology (2023) 143, 2484-2493

Advancing Researches on the Skin Microbiome of AD



* The articles marked in red are the research works of our team

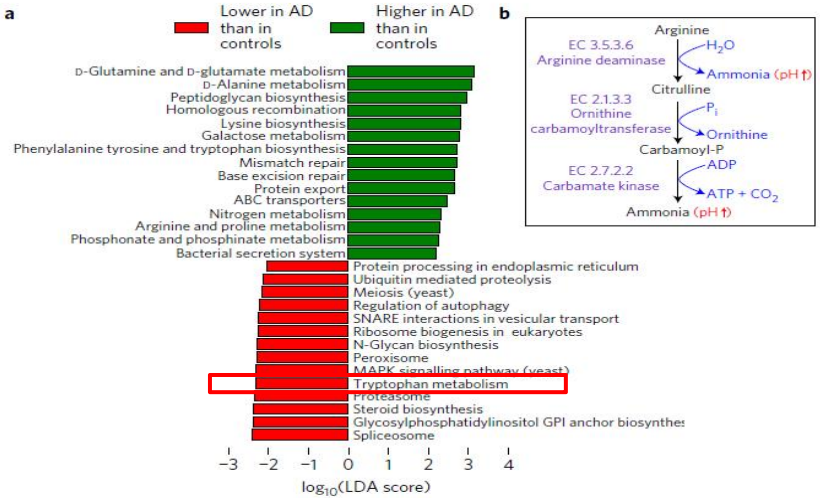
Skin Microbiota Metabolism in AD

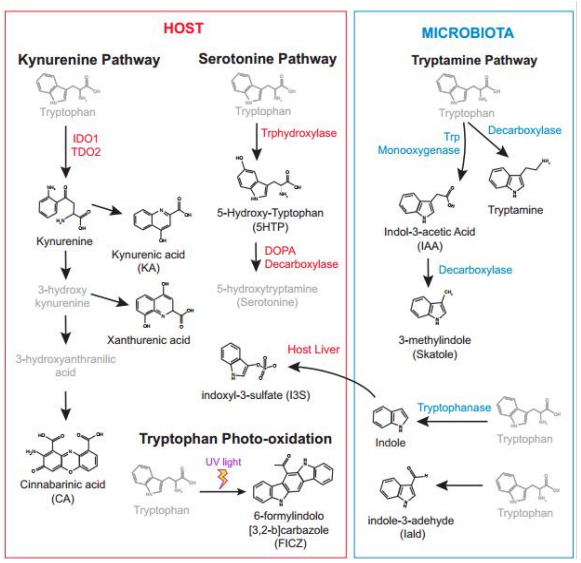
nature microbiology

ARTICLES

PUBLISHED: 11 JULY 2016 | ARTICLE NUMBER: 16106 | DOI: 10.1038/NMICROBIOL.2016.106

Whole metagenome profiling reveals skin microbiome-dependent susceptibility to atopic dermatitis flare



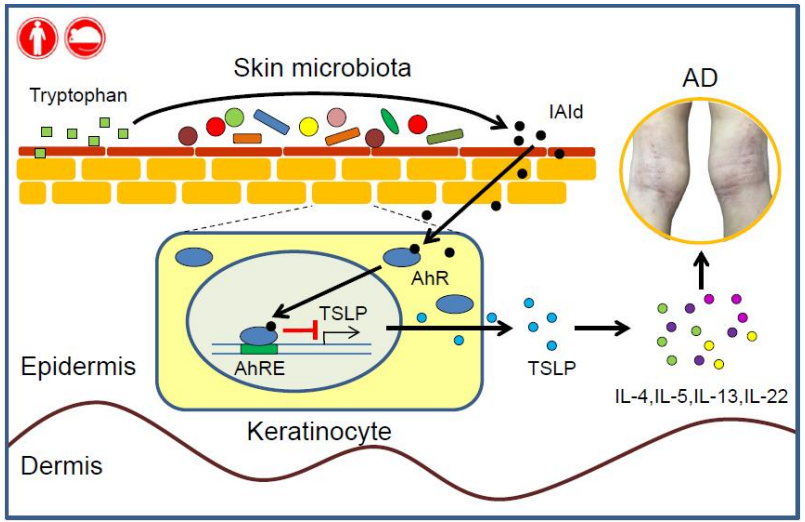


Main metabolites: Indole and indole derivatives

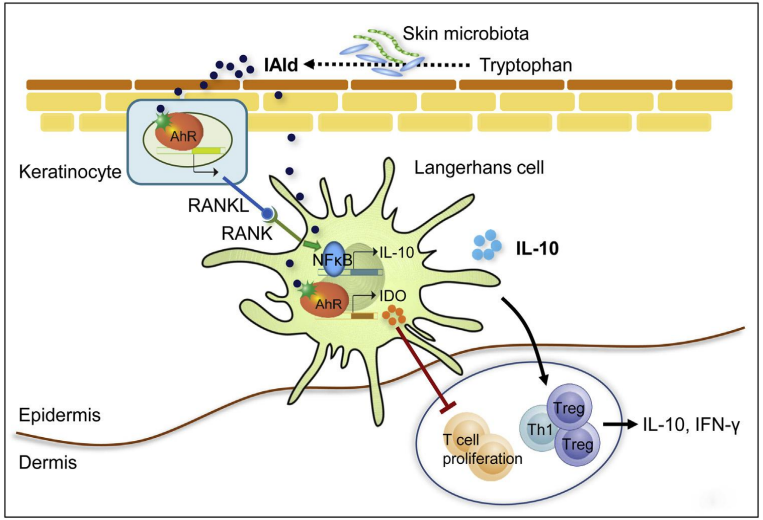
Nat Microbiology. 2016; 1:1

Cristina Gutie´rrez-Vazquez,2018,Immunity

Tryptophan Metabolite IAId from Skin Microbiota Regulates AD Inflammation



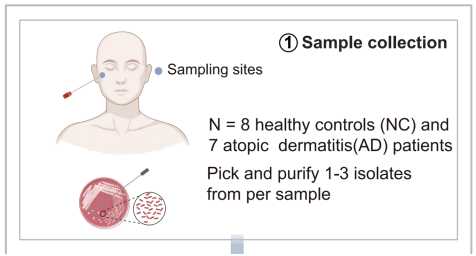
- The tryptophan metabolite IAId from skin microbiota acts on keratinocytes via the AhR, inhibiting TSLP and thereby suppressing AD inflammation

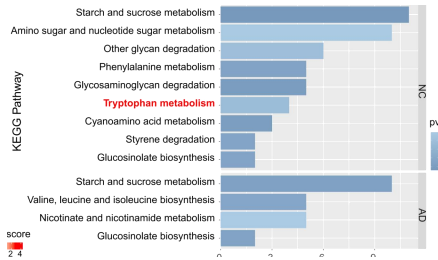


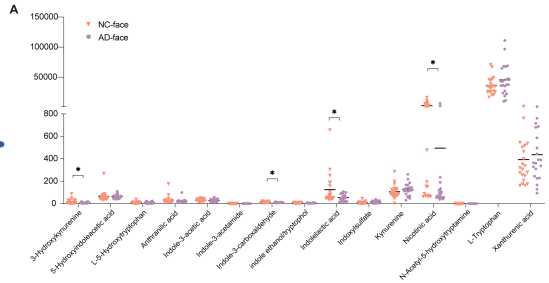
- IAId promotes RANK expression on Langerhans cells (LC) , and further inducing IL-10 and IDO production, which stimulates Treg proliferation.

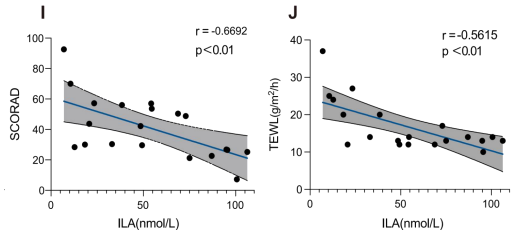
Yu et al. J Allergy Clin Immunol. 2019;143:2108-19.
X Liu, et al.Journal of Dermatological Science 100 (2020) 192–200

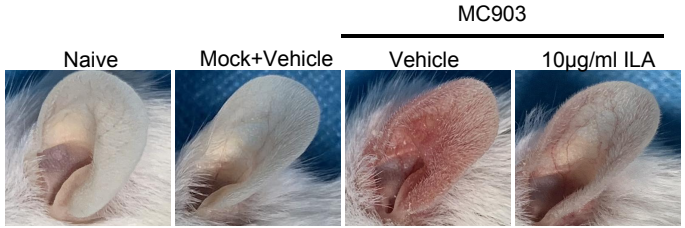
Tryptophan metabolite ILA from *C. acnes* regulates AD inflammation

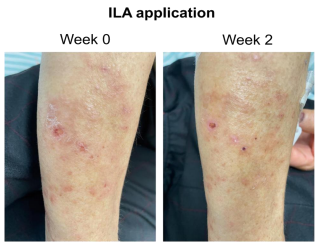








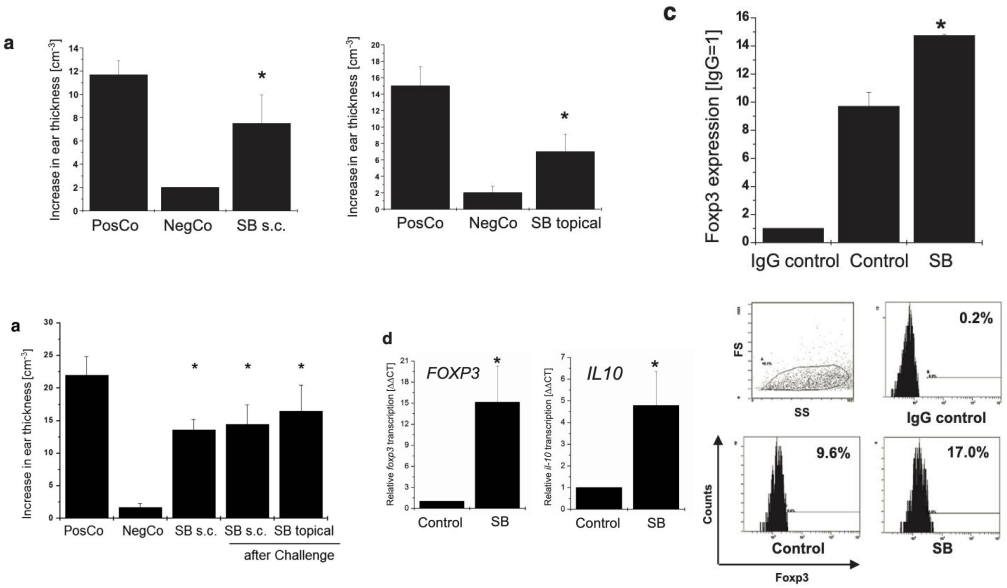


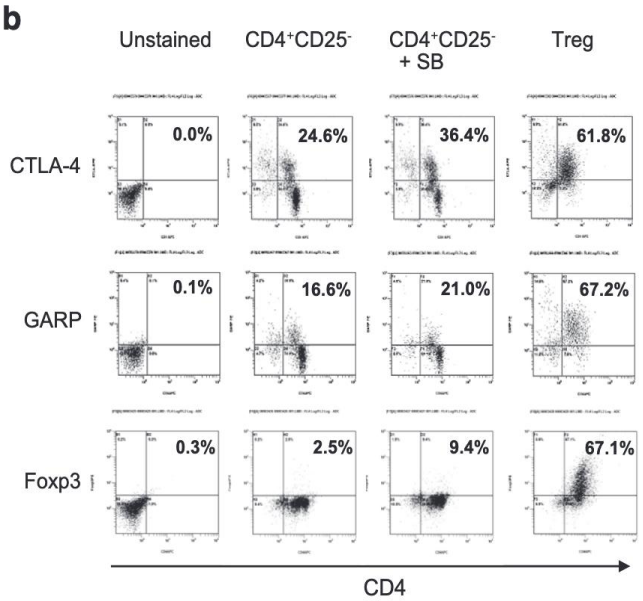


- ILA, as a major tryptophan metabolite of *C. acnes* has important functions on the repairment of skin barrier and attenuation of AD inflammation by activating the AhR pathway in KCs.

Shan Zhang et al. Cell Reports Medicine. In revision

SCFA-Sodium Butyrate Mitigate Inflammatory Skin Reactions



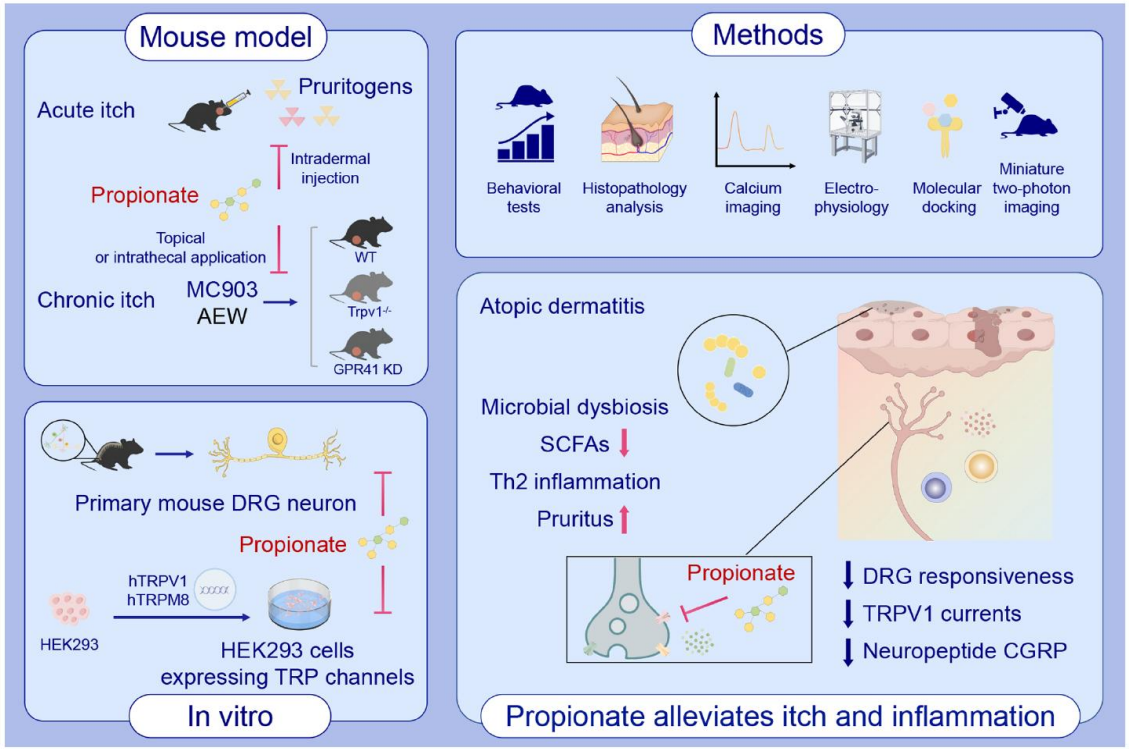


- Sodium butyrate (SB) inhibited the elicitation phase and ongoing response of contact hypersensitivity.
- SB induced skin Tregs and expression of IL-10.

- SB conversed non-regulatory T cells to a regulatory phenotype.

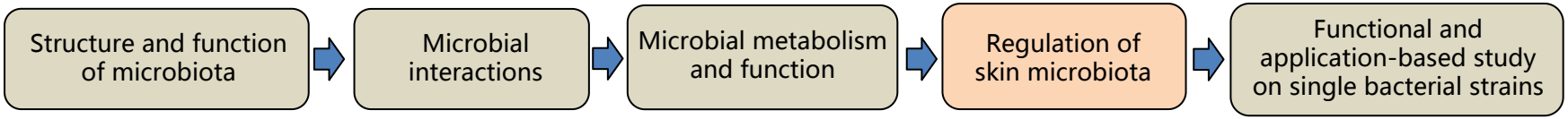
Schwarz A, et al. J Invest Dermatol. 2017 Apr;137(4):855-864.

Propionic acid acts on TRP channels in DRG to inhibit itching in AD mice



Xu Y, et al. **Allergy. 2024; 79(5): 1271-1290**

Advancing Researches on the Skin Microbiome of AD



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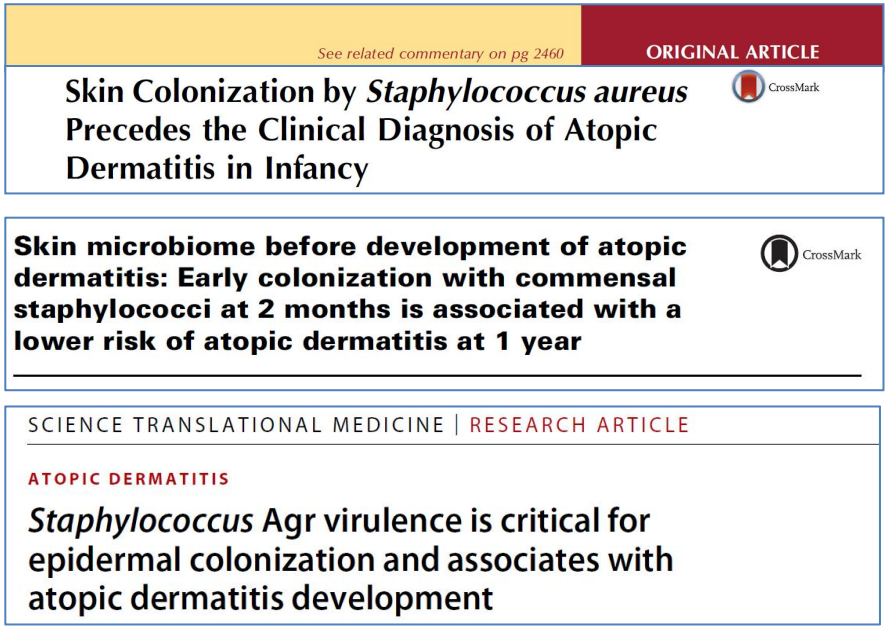
Does the Skin Microbiota Shift Precede the Skin inflammation in AD?



See related commentary on pg 2460

ORIGINAL ARTICLE

Skin Colonization by *Staphylococcus aureus* Precedes the Clinical Diagnosis of Atopic Dermatitis in Infancy

CrossMark

Skin microbiome before development of atopic dermatitis: Early colonization with commensal staphylococci at 2 months is associated with a lower risk of atopic dermatitis at 1 year

CrossMark

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

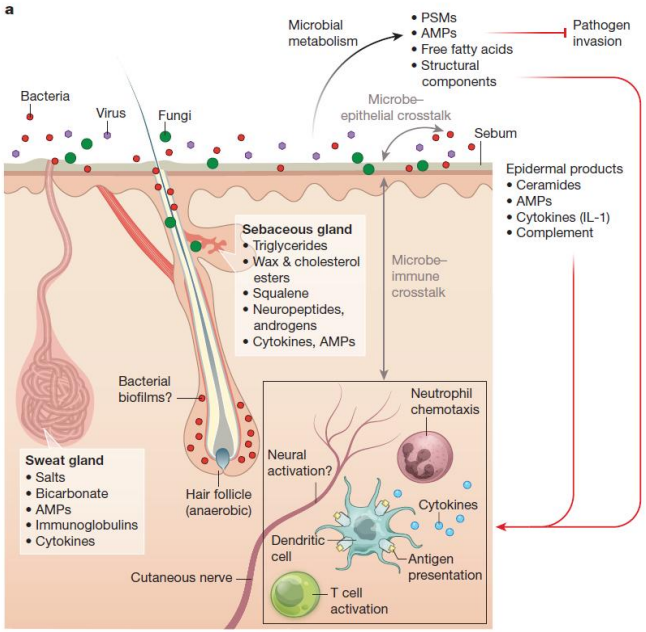
ATOPIC DERMATITIS

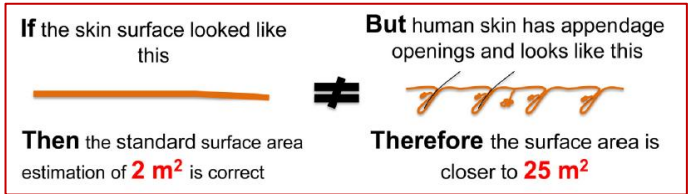
Staphylococcus Agr virulence is critical for epidermal colonization and associates with atopic dermatitis development

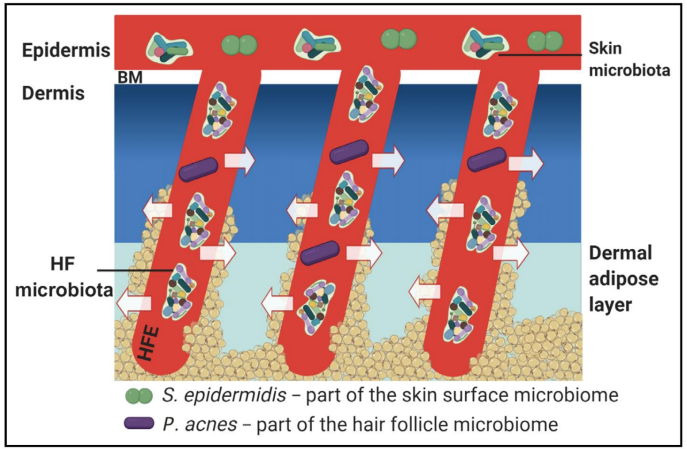
- The skin microbiota has already altered before the skin lesions.
- What triggers the initial shift in the skin microbiota?

Meylan P, et al. J Invest Dermatol 2017.
J Allergy Clin Immunol. 2017;139:166-72.
Nakamura et al. Sci Transl Med. 2020; 12, eaay4068

Key factor influencing the skin microbiota: The pilosebaceous unit





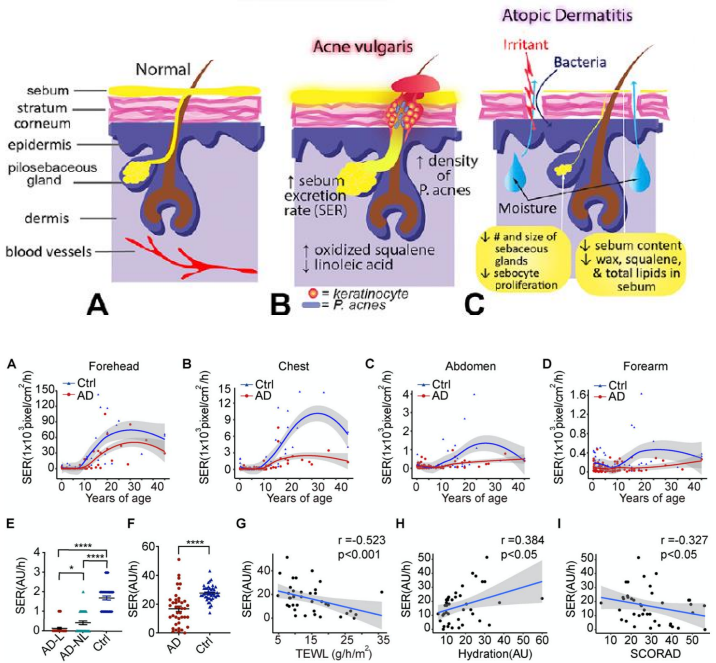


- Hair follicles provide an interface for the microbiota to interact with various layers of the skin.
- Different compartments of the pilosebaceous unit create distinct ecological niches for the microbiota.

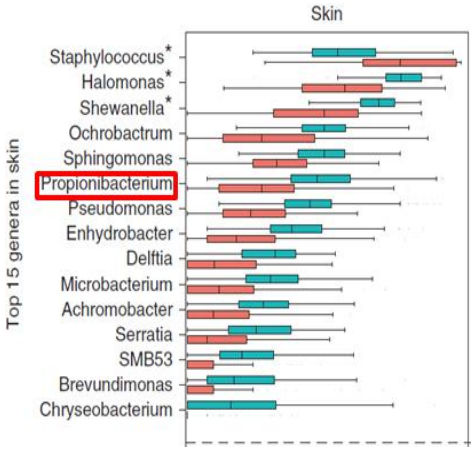
Nature. 2018(553):427.JID. 2017(137):1213

Sebaceous Glands and AD: An Emerging Field

Abnormal sebaceous gland in AD



Reduction of C.acne

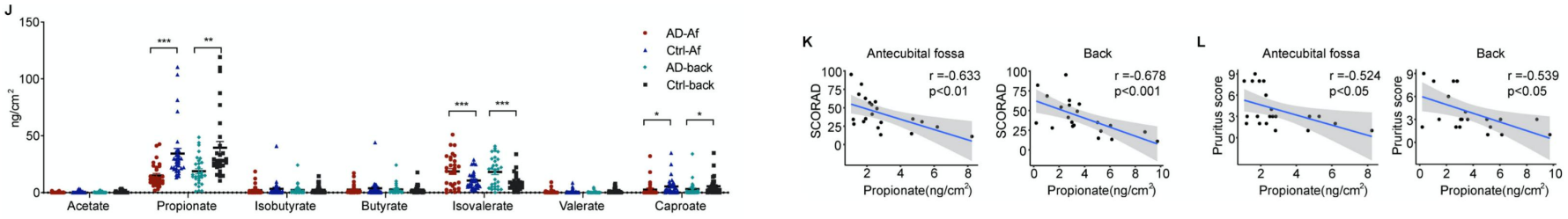


Abnormal lipid metabolism of the microbiota

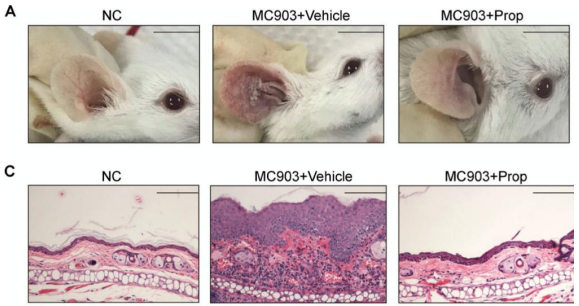
- Atrophy of sebaceous glands and downregulation of the secretory ability are very common in AD patients
- Sebum levels are correlated with disease severity.

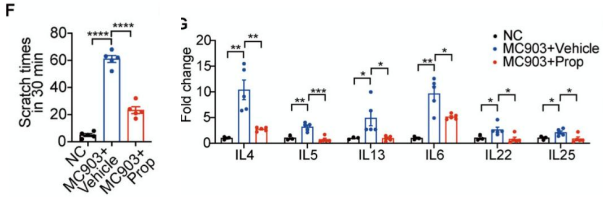
Li et al. J. Invest. Dermatol. 2019.
Shi VY, et al. *J Am Acad Dermatol* 2015.
Qiu Z, et al. J Exp Med. 2022 Oct 3;219(10):e20212397

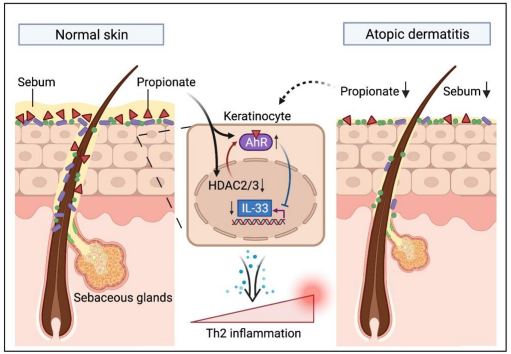
Dysregulation of "Sebum–Propionate –IL-33" Axis in AD



- The level of propionic acid on the skin is markedly lower than in healthy individuals and is correlated with disease severity



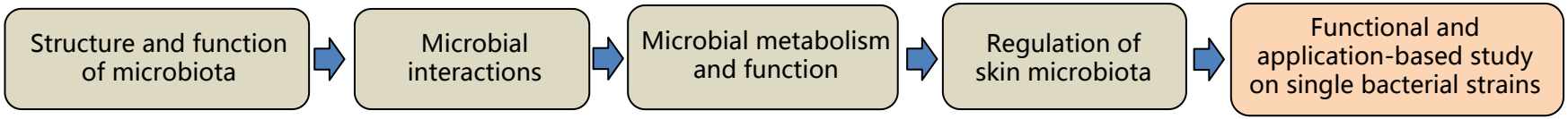




- In AD mice, propionic acid supplementation reduces skin inflammation
- Propionic acid inhibits keratinocyte (KC) production of IL-33 by promoting the expression and nuclear translocation of AhR

Qiu Z, et al. J Exp Med. 2022 Oct 3;219(10):e20212397

Advancing Researches on the Skin Microbiome of AD



* The articles marked in red are the research work of our team

Previous Studies are Mainly Focused on Immunity, Barrier, Traumer and Diseases

MICROBIOLOGY

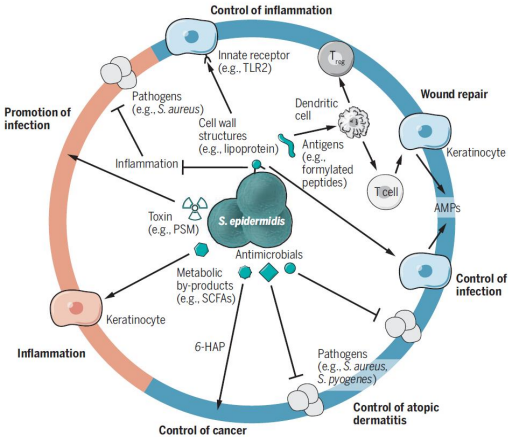
Microbial guardians of skin health

Skin microbes can promote skin immunity, repair, and antimicrobial defense

By **Apollo Stacy**[4,5,6] *and* **Yasmine Belkaid**[1,2] | they peacefully coexist with the skin micro- | cells are noted for acquiring target specific-

The multifaceted roles of *S. epidermidis* in skin physiology

S. epidermidis guards skin against inflammation, infections, and cancer through interactions with keratinocytes, T cells, and other members of the skin microbiota. These interactions are strain- and context-dependent, with some leading to negative outcomes for the host, including inflammation and infection.

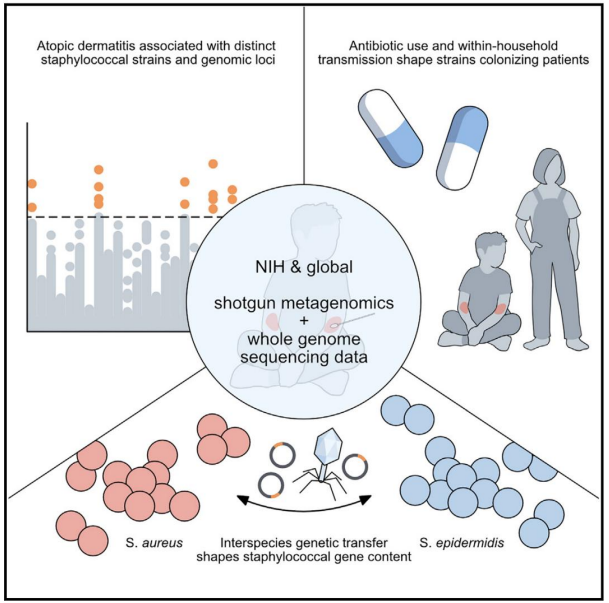


Science. 2019; 363(6424): 227-228.

Article

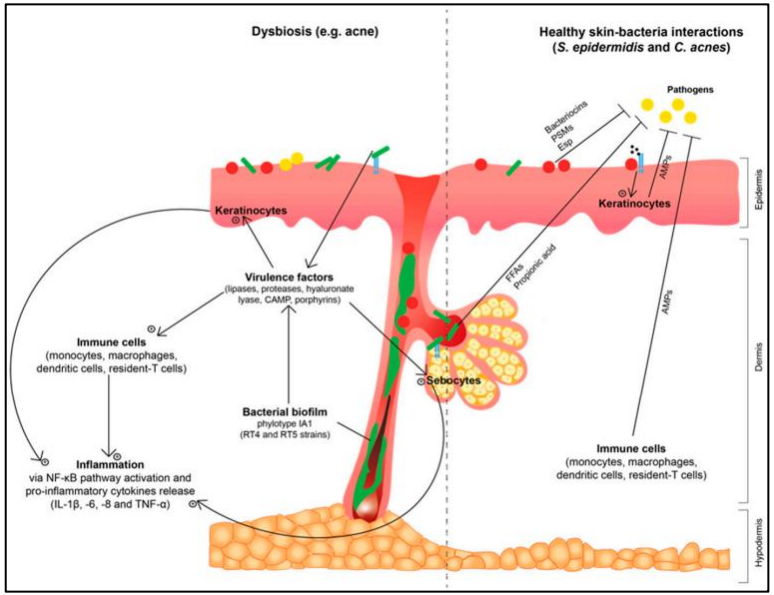
Cell Host & Microbe

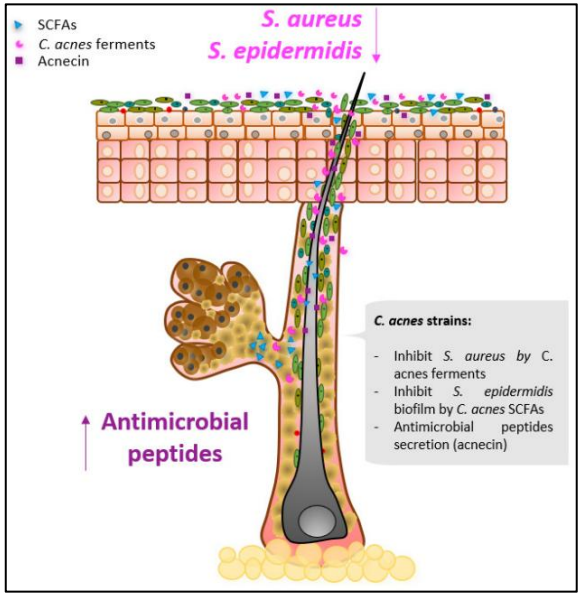
Staphylococcal diversity in atopic dermatitis from an individual to a global scale



Cell Host Microbe. 2023;31(4.):578-592.

C. acnes：the Most Abundant Bacteria in the Skin

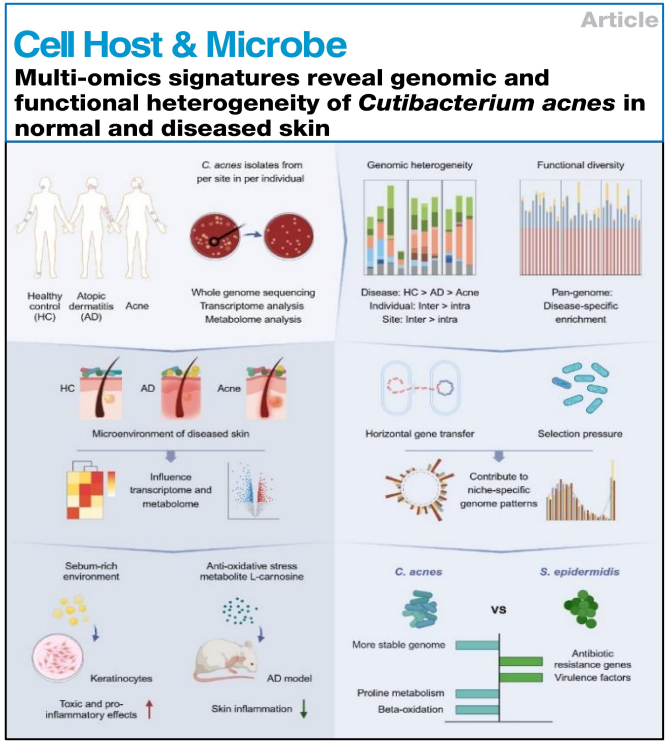




- *C. acnes* secretes SCFAs to regulate skin pH。
- *C. acnes* secretes thiopeptide antibiotics to resist *S. aureus* colonization.
- *C. acnes* induces the host to secrete antimicrobial peptides such as β-defensin-2.

Rozas et al. Microorganisms. 2021
Fournière et al. Microorganisms. 2020

Single-Strain Multi-Omics Analysis Reveals the Genetic and Functional Heterogeneity of *C. acnes*



1. Skin disease and person- and site-specific features shape *C. acnes* genomic differences
2. Horizontal gene transfer and selection pressure contribute to *C. acnes* genome patterns
3. *C. acnes* lacks most virulence genes compared with *S. epidermidis*
4. Niches influence the transcriptome/metabolome signatures and functions of *C. acnes*

Yu, et al. Cell Host Microbe. 2024 Jul 10;32(7):1129-1146.

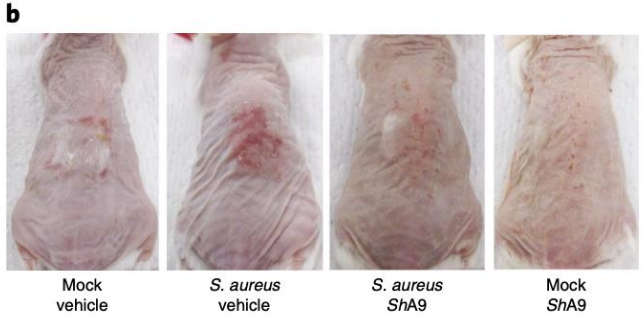
Application of Commensal Staphylococci against *S. aureus* in the Treatment of AD

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01256-2
Check for updates

Development of a human skin commensal microbe for bacteriotherapy of atopic dermatitis and use in a phase 1 randomized clinical trial

Teruaki Nakatsuji[1], Tissa R. Hata[1], Yun Tong[1], Joyce Y. Cheng[1], Faiza Shafiq[1], Anna M. Butcher[1], Secilia S. Salem[1], Samantha L. Brinton[1], Amanda K. Rudman Spergel[2], Keli Johnson[3], Brett Jepson[3], Agustin Calatroni[3], Gloria David[3], Marco Ramirez-Gama[4], Patricia Taylor[4], Donald Y. M. Leung[4] and Richard L. Gallo[1]✉

- Topical application of *S. hominis* ShA9, a human commensal strain with anti-*S. aureus* activity, onto AD mouse models killed *S. aureus* and suppressed Psmα production.
- A Phase I clinical study of topical ShA9 application on skin lesions of AD patients demonstrated a favorable safety profile.



Nakatsuji et al. Nat Med. 2021;27(4):700-709.

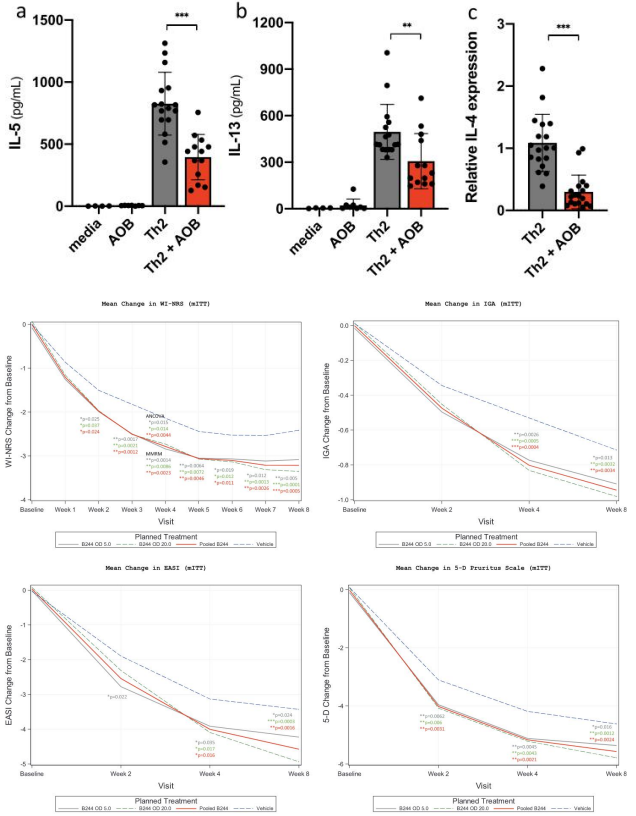
Application of Nitrosomonas B244 in the Treatment of AD

eClinicalMedicine
Part of THE LANCET *Discovery Science*

Efficacy and safety of topically applied therapeutic ammonia oxidising bacteria in adults with mild-to-moderate atopic dermatitis and moderate-to-severe pruritus: a randomised, double-blind, placebo-controlled, dose-ranging, phase 2b trial

Jonathan I. Silverberg,[a] Peter A. Lio,[b] Eric L. Simpson,[c] Connie Li,[d] Daniel R. Brownell,[d] Ioannis Gryllos,[d] Judith Ng-Cashin,[d] Todd Krueger,[d] Victoria R. Swaidan,[e] Robin L. Bliss,[f] and Hyun D. Kim[d,]*

- B244 is an ammonia-oxidizing bacterium of the genus *Nitrosomonas*, isolated and purified from soil.
- B244 can inhibit the growth of *S. aureus* and reduce levels of type 2 cytokines (IL-4, IL-5, and IL-13).
- A Phase 2 clinical trial demonstrated that B244 treatment led to an average reduction in the IGA and EASI scores.



Maura D, et al. Sci Rep. 2021
Silverberg JI, et al. EClinicalMedicine. 2023

Application of microbiota metabolite AD101 for AD treatment

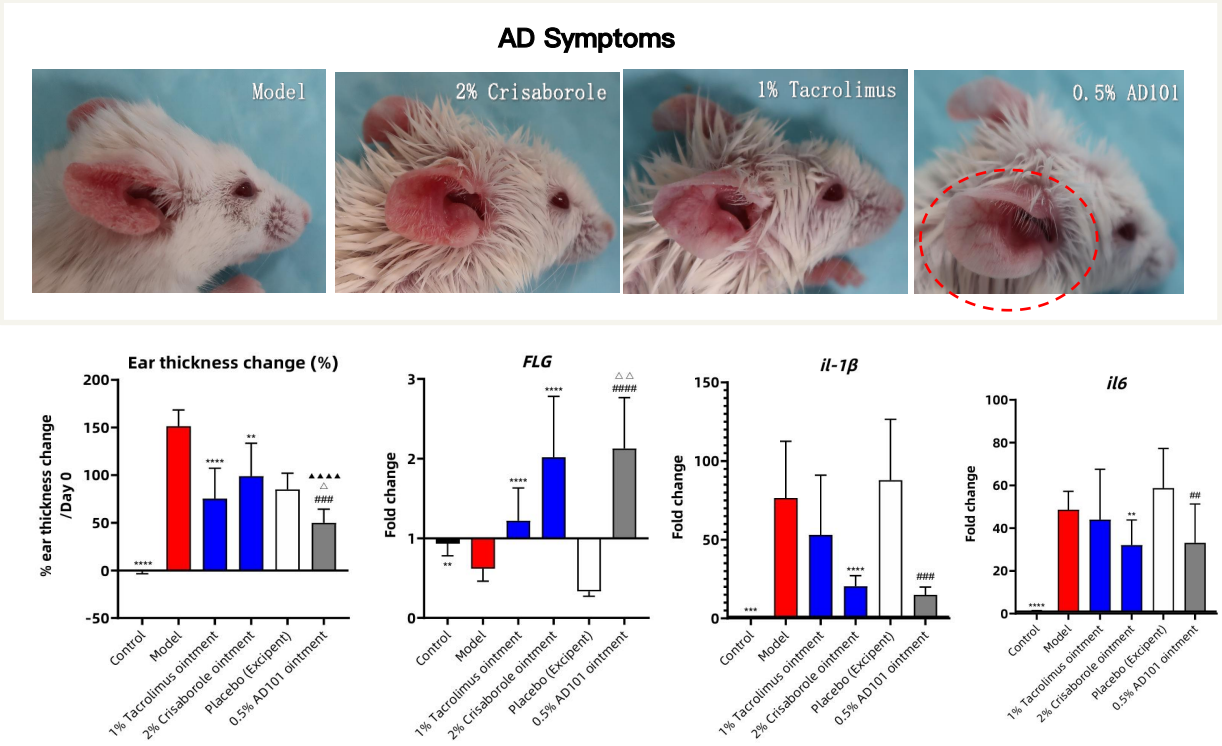
microbiota metabolite IAID

optimization and reformation(AD101)

Validation in cells and mice

Preclinical study

Clinical study(Phase 1-Phase 2)



Undisclosed data

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Zhuoqiong Qiu, Tianze Yu, Yao Xu, Xiaoqiang Xu, Ronghui Zhu, Shang shang Wang

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- Major Project of the Shanghai Municipal Education Commission's Scientific Research Innovation Program