Ref No. : OL9

EGFR-mediated autophagy by betacellulin improves atopic dermatitis pathogenesis

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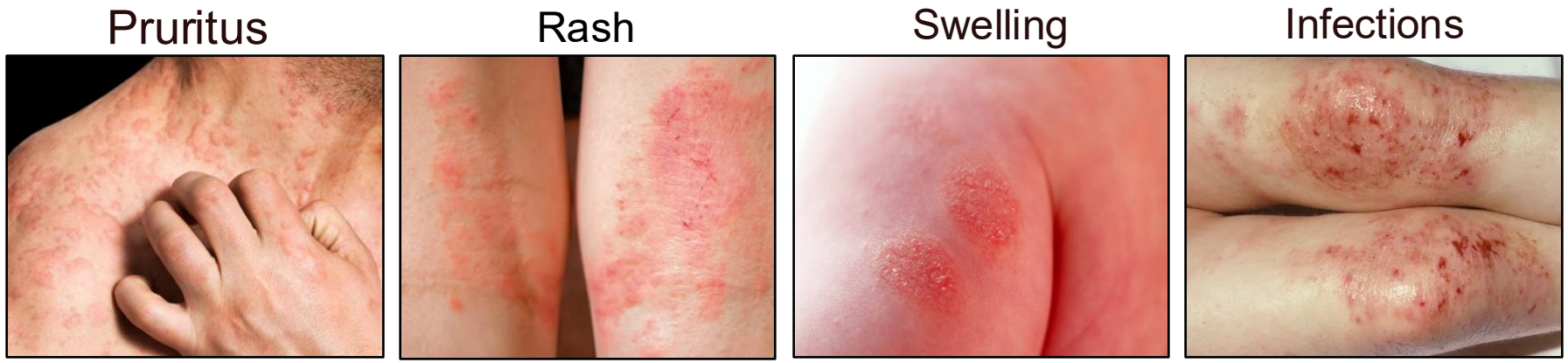
Melbourne 2025
Georg RAJKA — ISAD

Melbourne 2025
Georg RAJKA — ISAD
COI Disclosure
Ge Peng, et al.

The authors have no financial conflicts of interest to disclose concerning the presentation.

Atopic dermatitis (AD)

- AD is the most common chronic inflammatory skin disease, with a lifetime prevalence of up to 20% and substantial effects on quality of life.
- Symptoms of AD

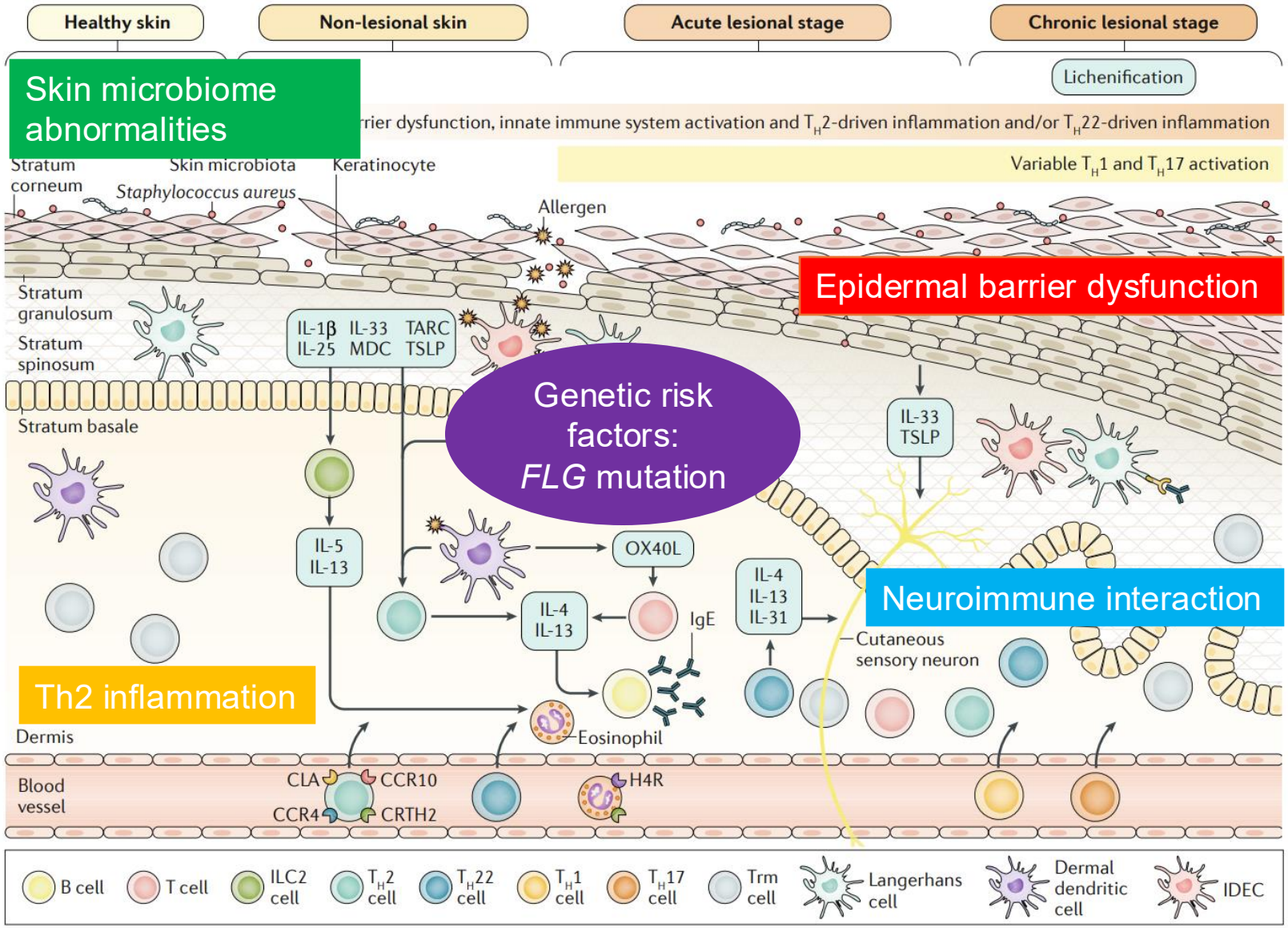


- Global epidemiology of atopic dermatitis

Around 101.27 million adults and 102.78 million children worldwide have AD, corresponding to prevalence rates of 2.0% and 4.0%, respectively.

Tian J, et al. *Br J Dermatol*. 2023

Pathogenesis of AD



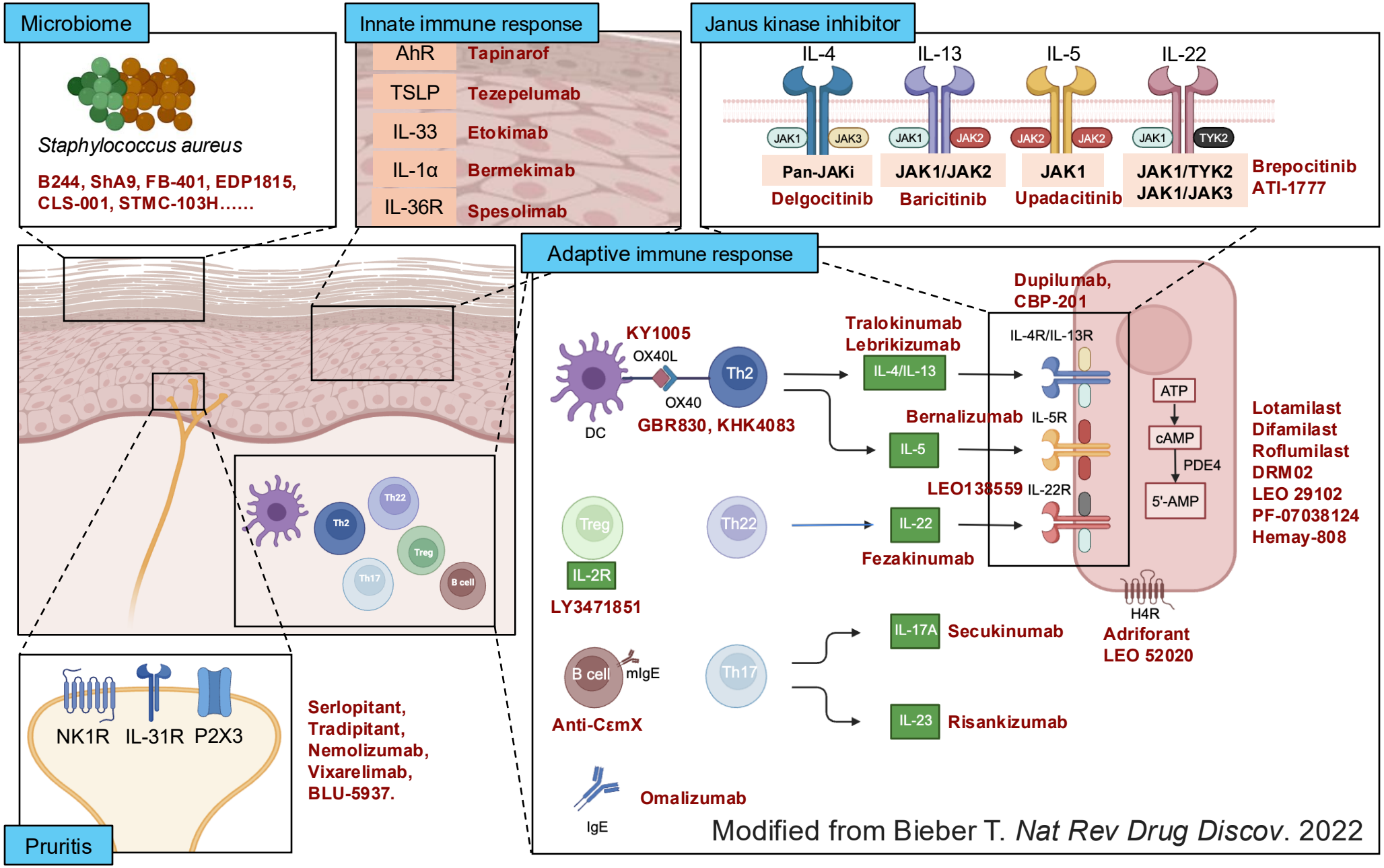
The pathophysiology of AD involves a complex interplay between:

- *FLG* gene mutation
- Dysfunctional epidermal barrier
- Skin microbiome abnormalities
- Type-2-skewed immune dysregulation
- Neuroimmune interaction

These mechanistic drivers can promote and interact with others.

Weidinger S. *Nat Rev Dis Primers*. 2018.

Therapeutic strategies for AD

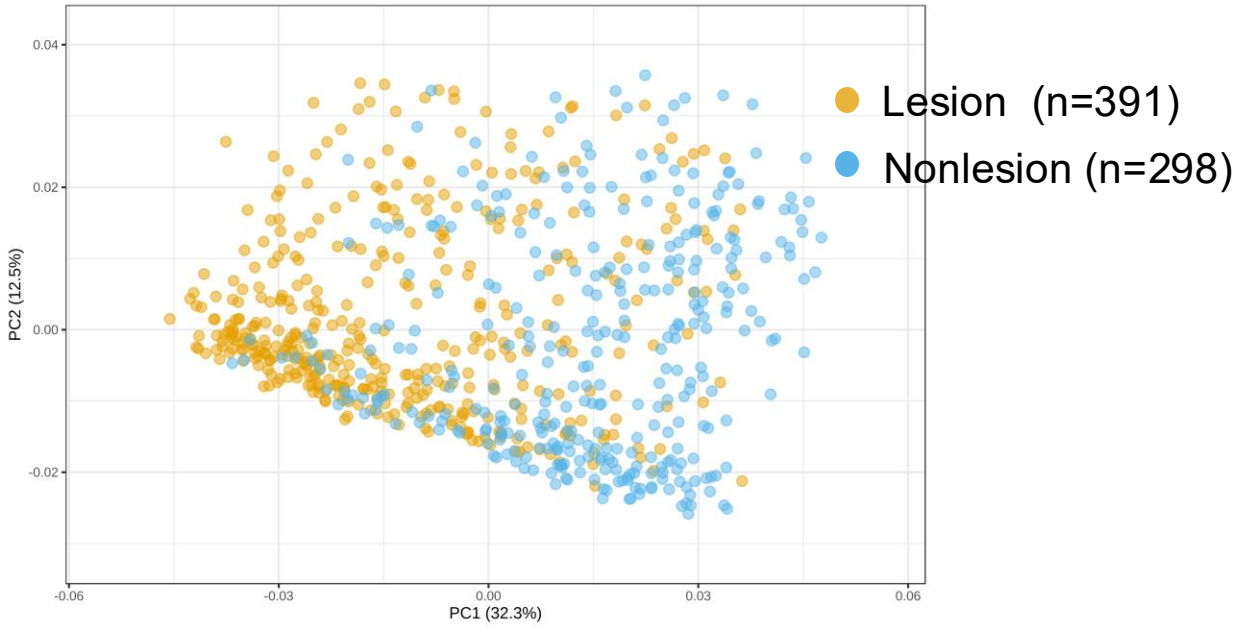


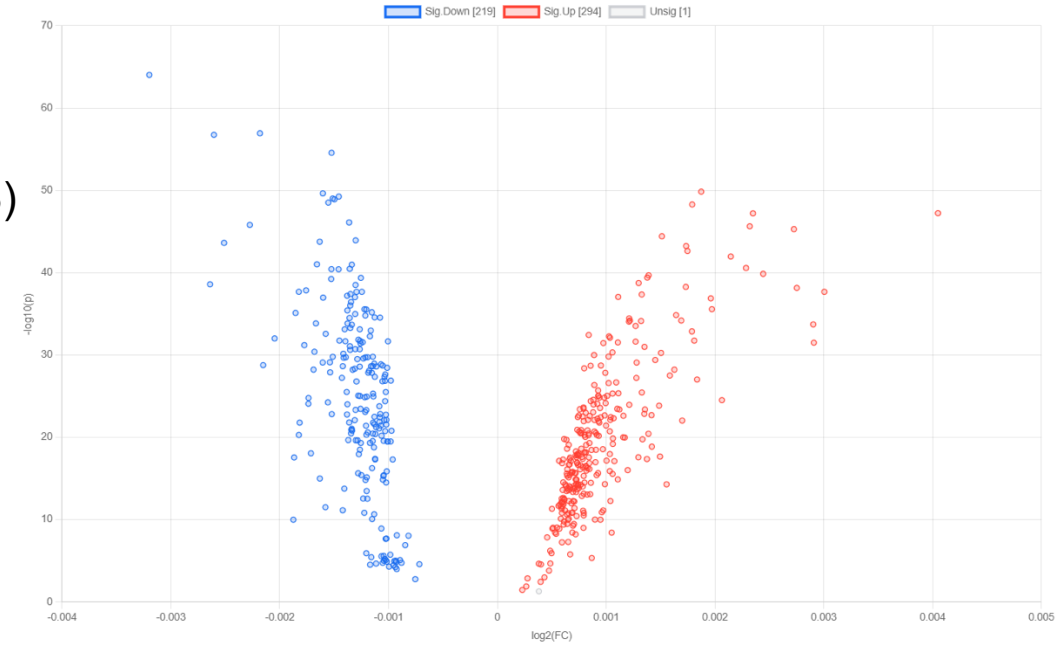
Modified from Bieber T. *Nat Rev Drug Discov*. 2022

Microarray data analysis of AD transcriptome

GEO dataset:
GSE59294
GSE32924
GSE36842
…

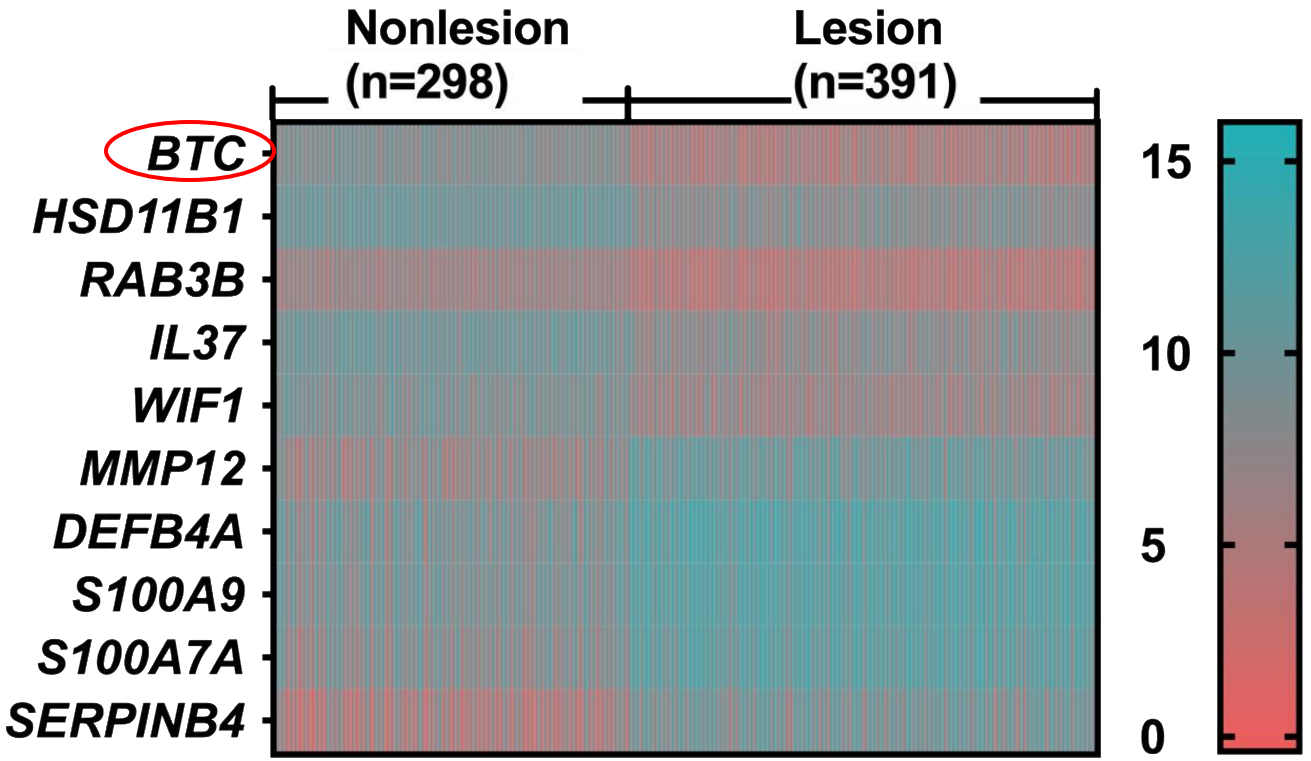
- Lesional skin
- Nonesional skin





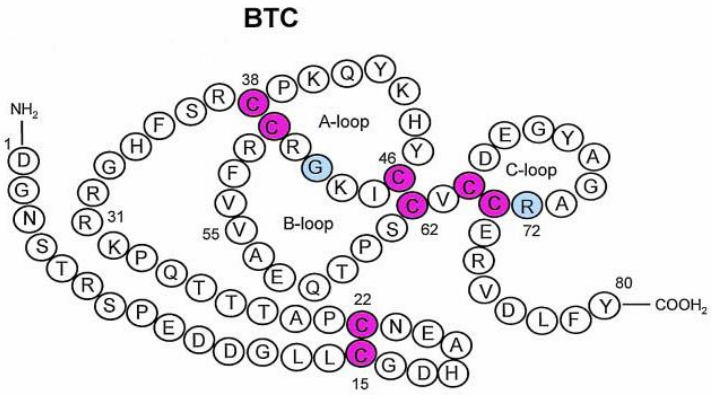
GEO: Gene Expression Omnibus; PCA: Principal component analysis

Betacellulin (BTC) is the most downregulated gene in AD skin lesions

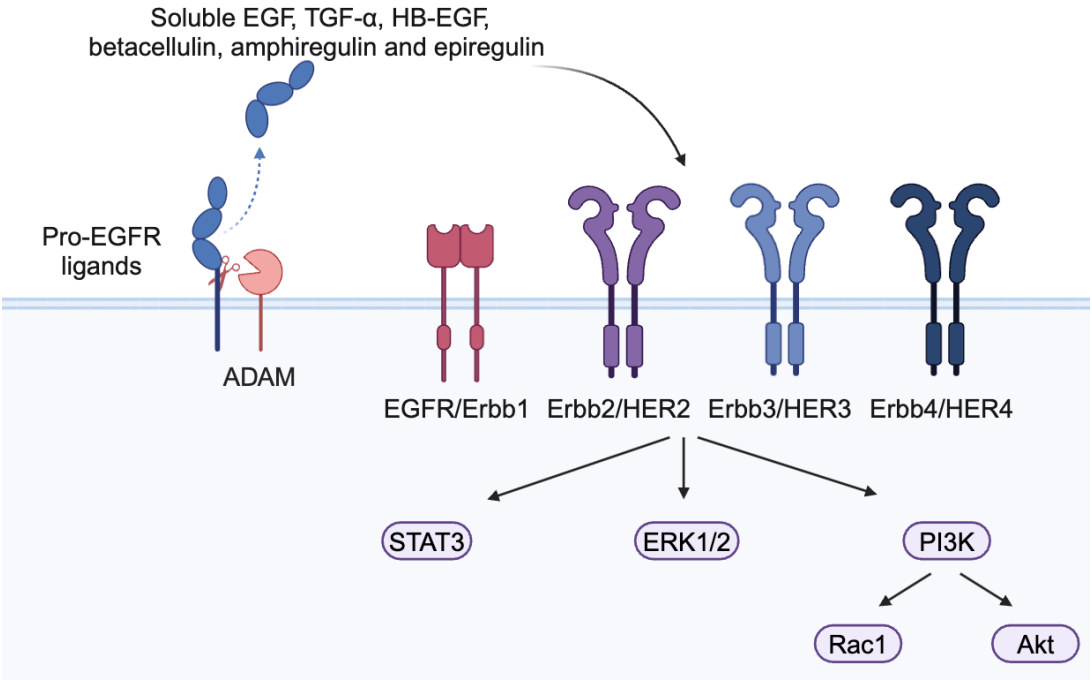


Peng G, et al. *Int J Mol Sci*. 2022.

Structure of BTC



Dunbar AJ. *Int J Biochem Cell Biol*. 2000.



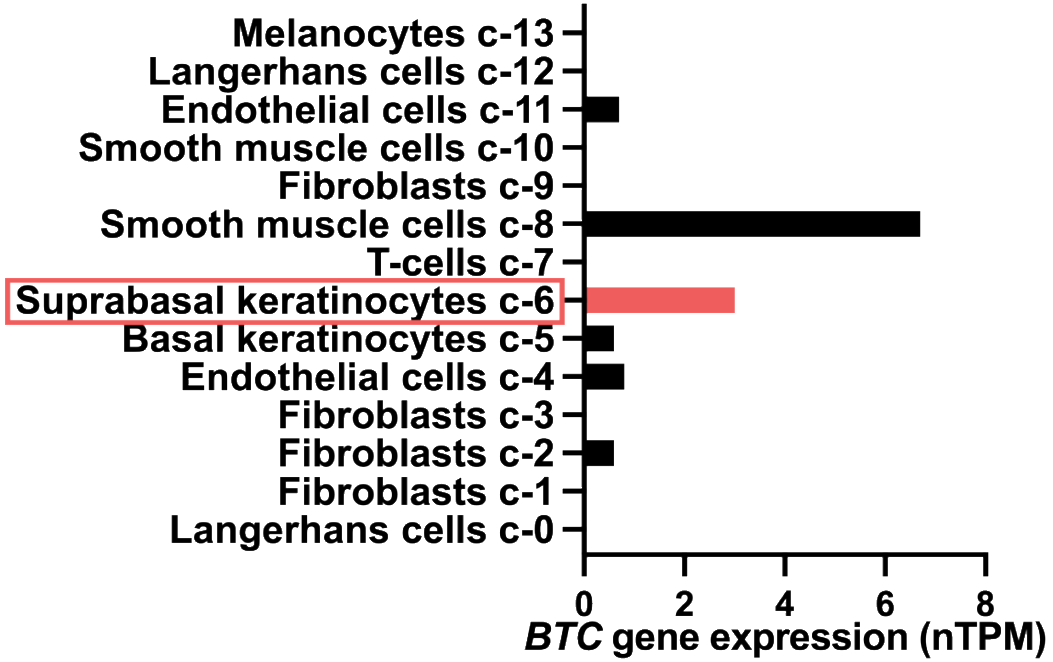
Modified from Nanba D. *J Dermatol Sci*. 2013.

- BTC belongs to the epidermal growth factor (EGF) family of peptide ligands that are characterized by a six-cysteine consensus motif which forms three intra-molecular disulfide bonds crucial for binding the ErbB receptor family.

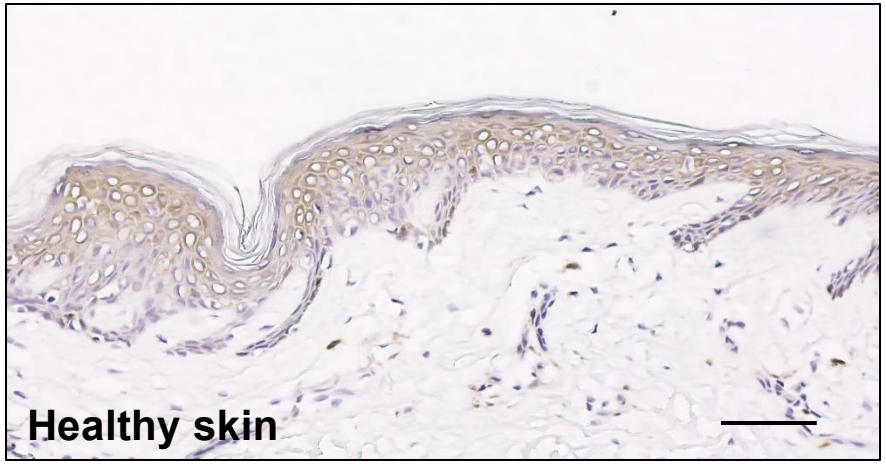
- Members of EGF family play important roles in skin morphogenesis, homeostasis and repair. However, the role of BTC in skin biology is unknown.

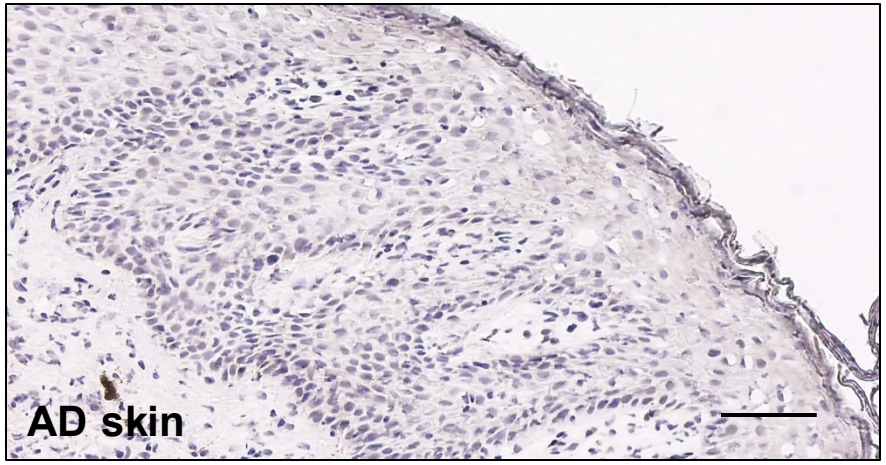
BTC is downregulated in AD

- Single-cell type analysis of normal human skin tissues from the HPA web server

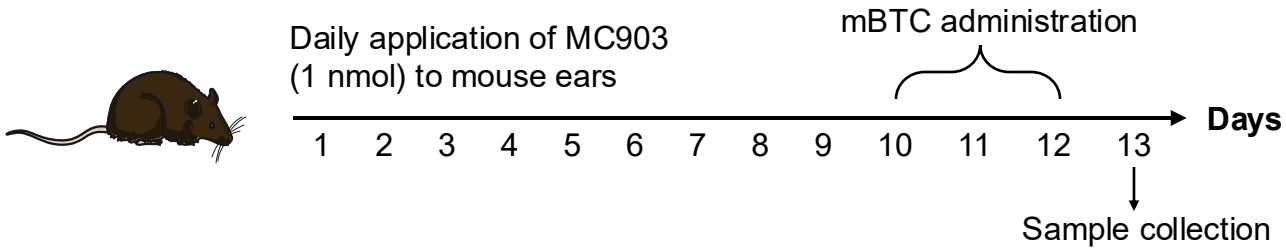


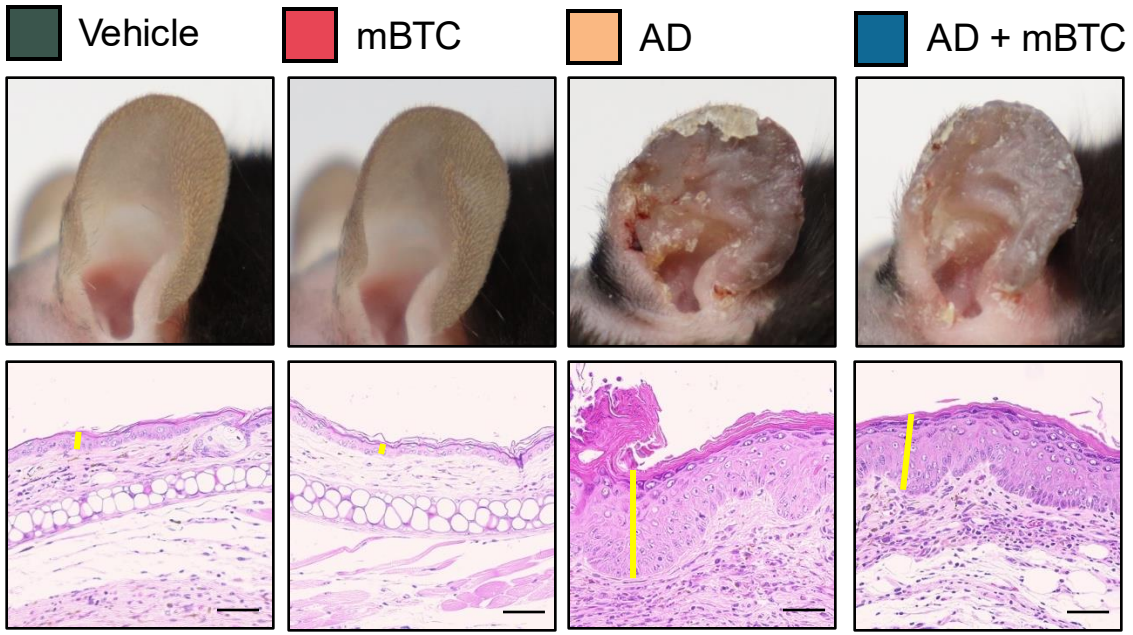
- Expression of BTC in the skin of AD patients

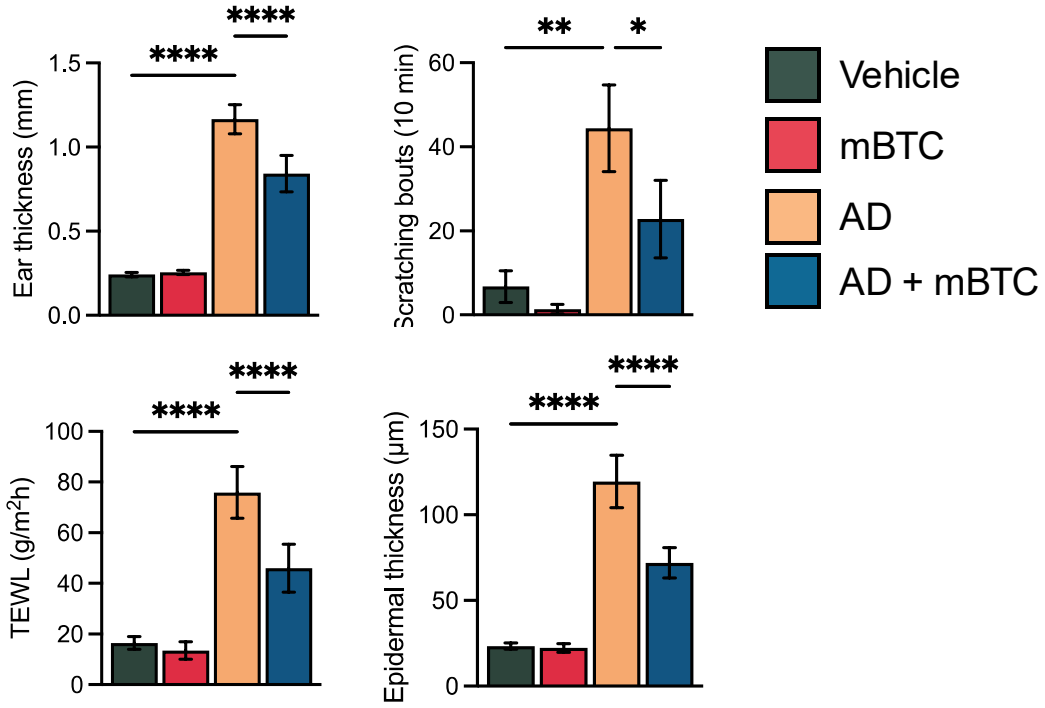




BTC alleviates MC903-induced AD-like symptoms in a murine model

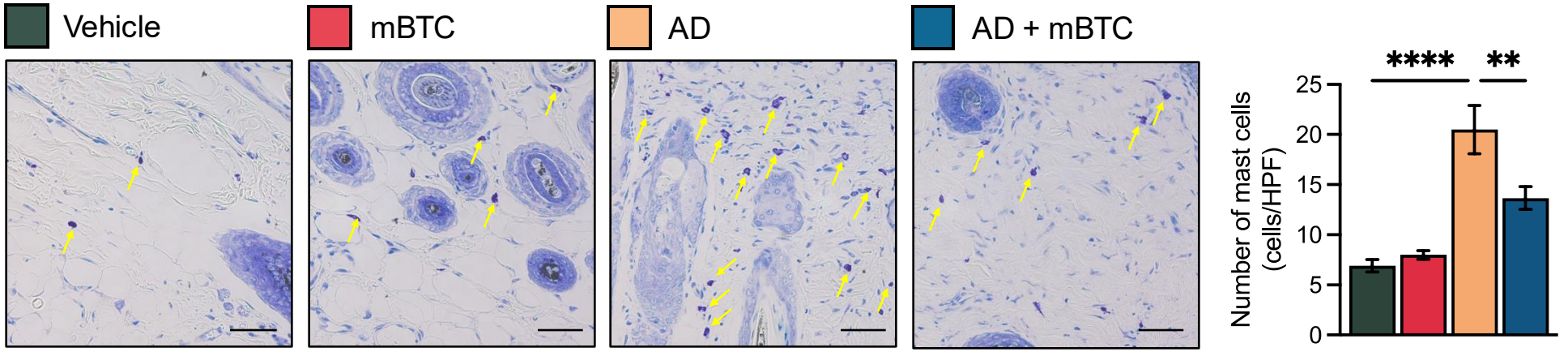






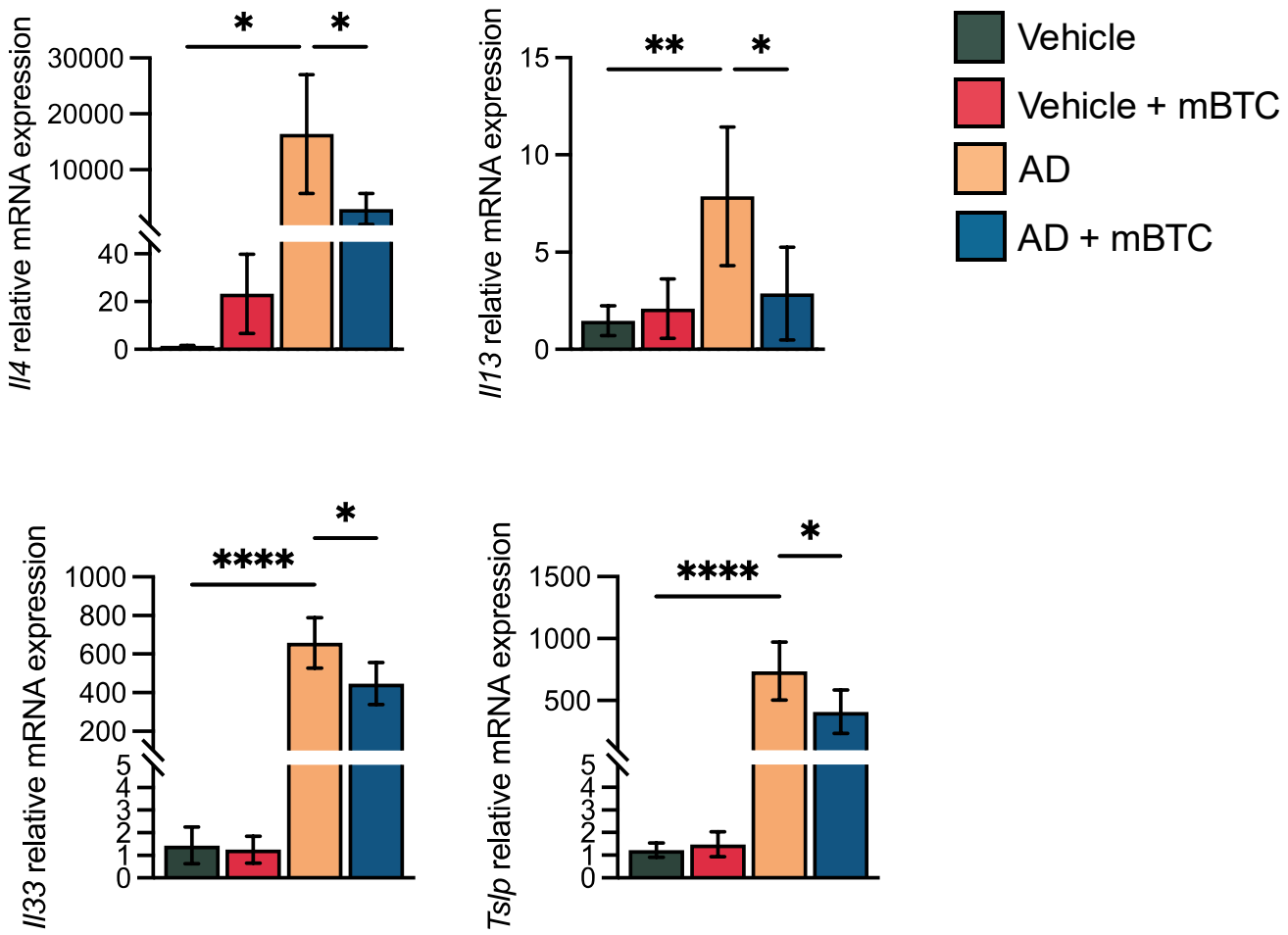
TEWL: transepidermal water loss

BTC reduces mast cell infiltration in an AD murine model

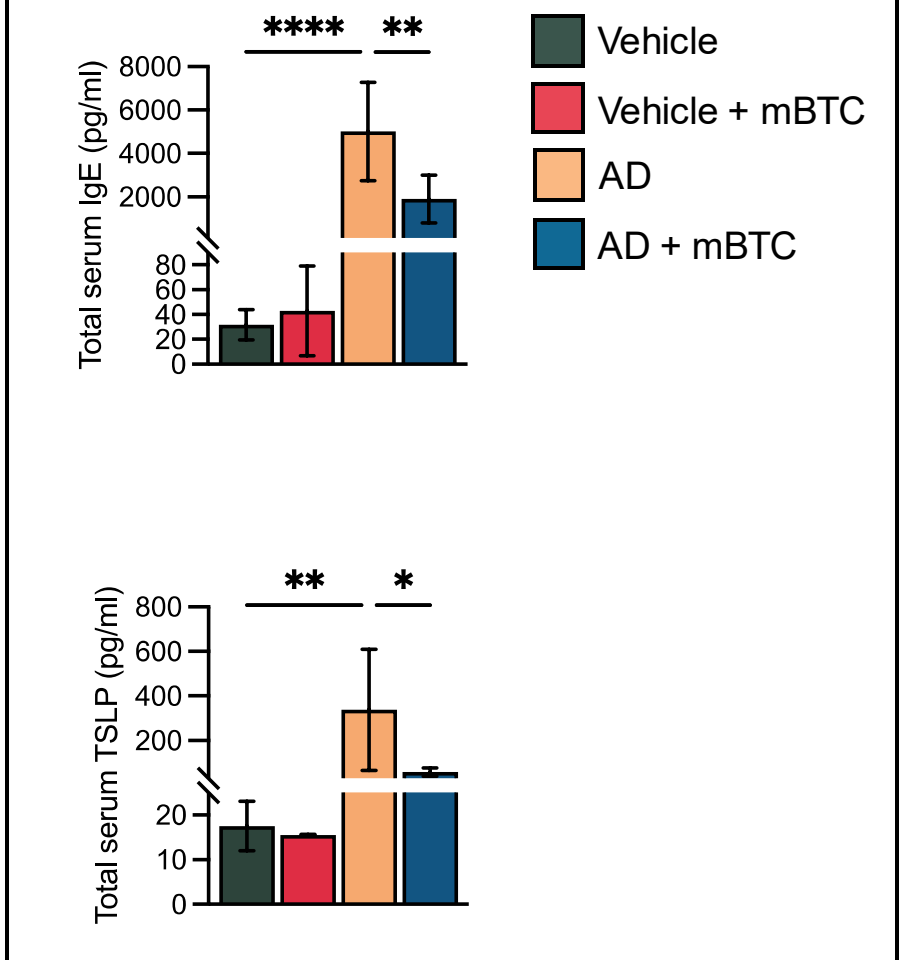


BTC suppresses inflammation in an AD murine model

Real-time PCR



ELISA



BTC suppresses inflammation in an AD murine model

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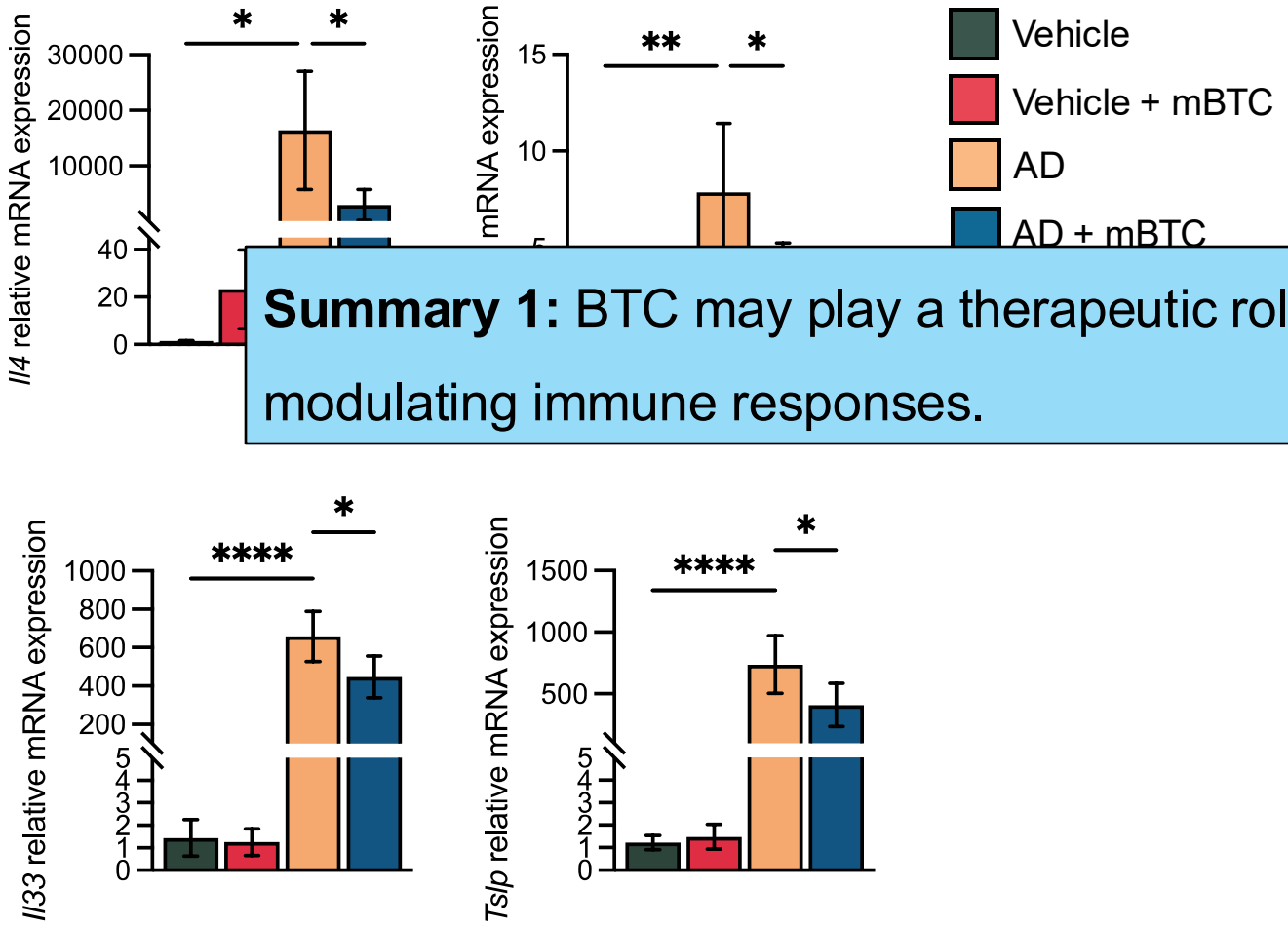
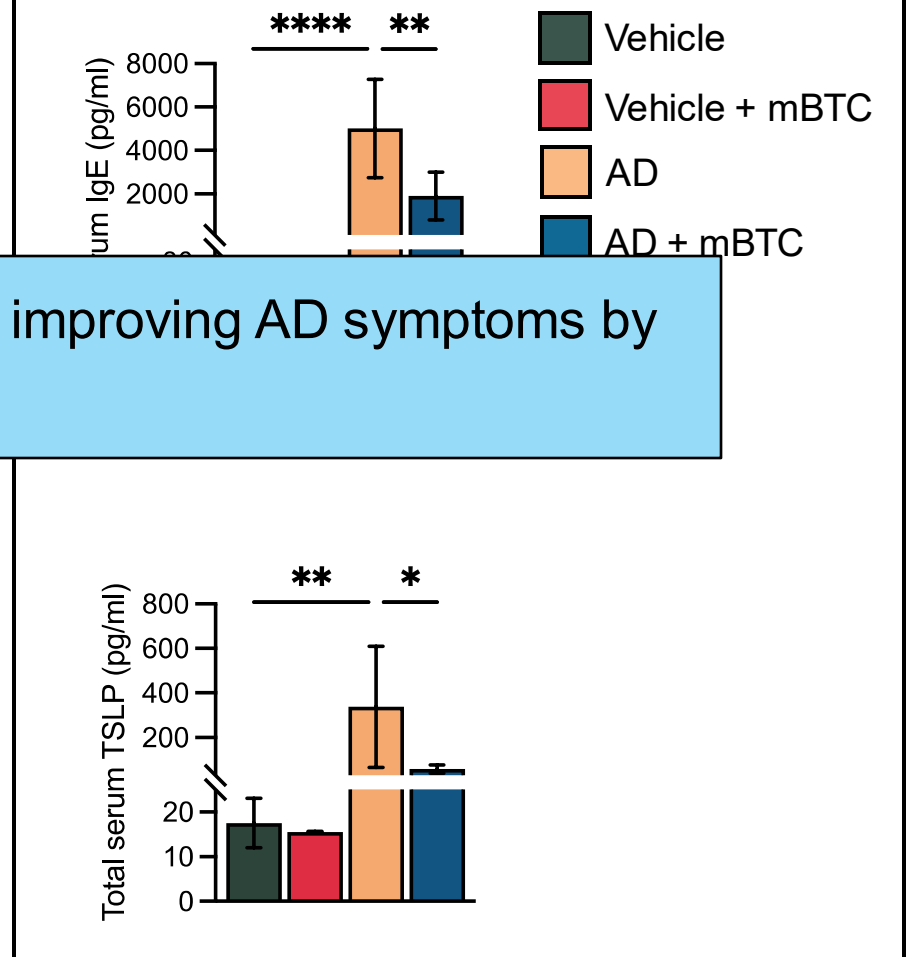
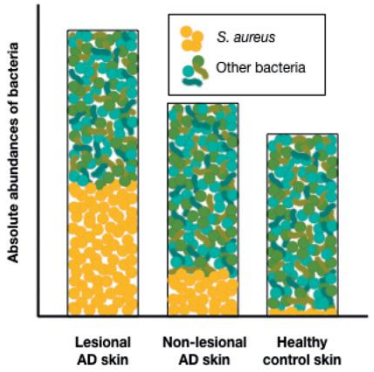
ELISA





Summary 1: BTC may play a therapeutic role in improving AD symptoms by modulating immune responses.

Staphylococcus aureus in AD



S. aureus commonly colonizes the skin of AD patients and contributes to the development and exacerbation of AD.

Edslev SM et al. *Acta Derm Venereol*. 2020.

Dysbiosis and *Staphyloccus aureus* Colonization Drives Inflammation in Atopic Dermatitis

Tetsuro Kobayashi,[1,2] Martin Glatz,[2] Keisuke Horiuchi,[3] Hiroshi Kawasaki,[1] Haruhiko Akiyama,[4] Daniel H. Kaplan,[5] Heidi H. Kong,[2] Masayuki Amagai,[1] and Keisuke Nagao[1,2,*]
[1]Department of Dermatology, Keio University School of Medicine, Tokyo, Japan, PC160-8582
[2]Dermatology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA
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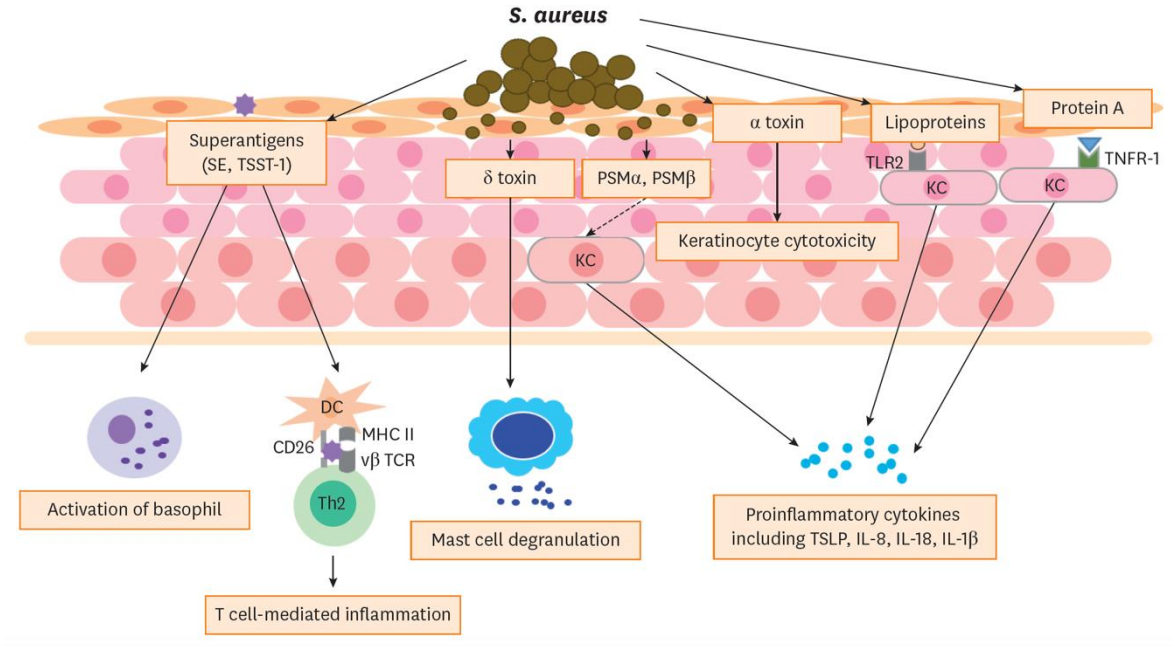
[4]Department of Orthopedics, Gifu University, Gifu, Japan, PC 501-1194
[5]Department of Dermatology, Center for Immunology, University of Minnesota, Minneapolis, MN 55414, USA
*Correspondence: keisuke.nagao@nih.gov
http://dx.doi.org/10.1016/j.immuni.2015.03.014

Kobayashi T et al. *Immunity*. 2015.



Kim J et al. *Allergy Asthma Immunol Res*. 2019.

S. aureus skin colonization is frequent in AD and common in cancer patients treated with EGFR inhibitors.

EGFR ligand：BTC

↓ ?

S. aureus

BTC does not show direct killing effect on *S. aureus*

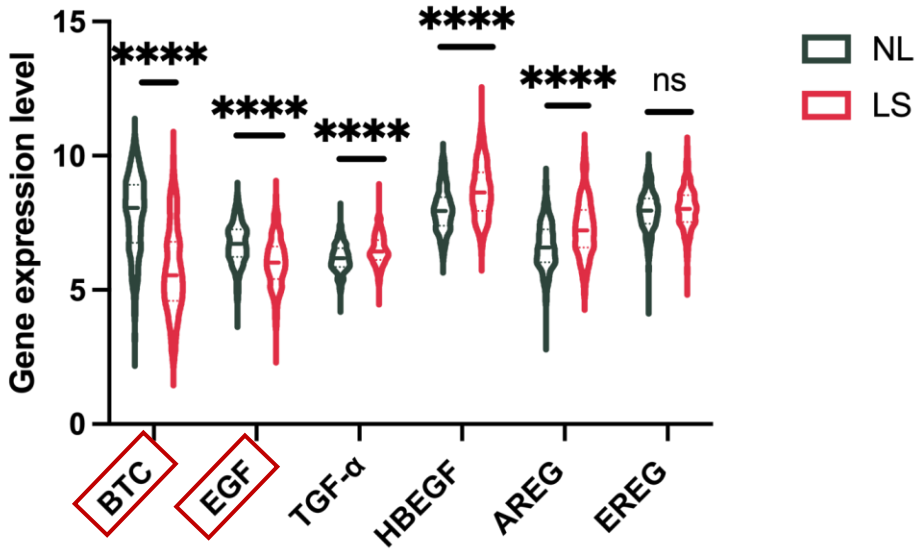
Research Article

Epidermal Growth Factor Relieves Inflammatory Signals in *Staphylococcus aureus*-Treated Human Epidermal Keratinocytes and Atopic Dermatitis-Like Skin Lesions in Nc/Nga Mice

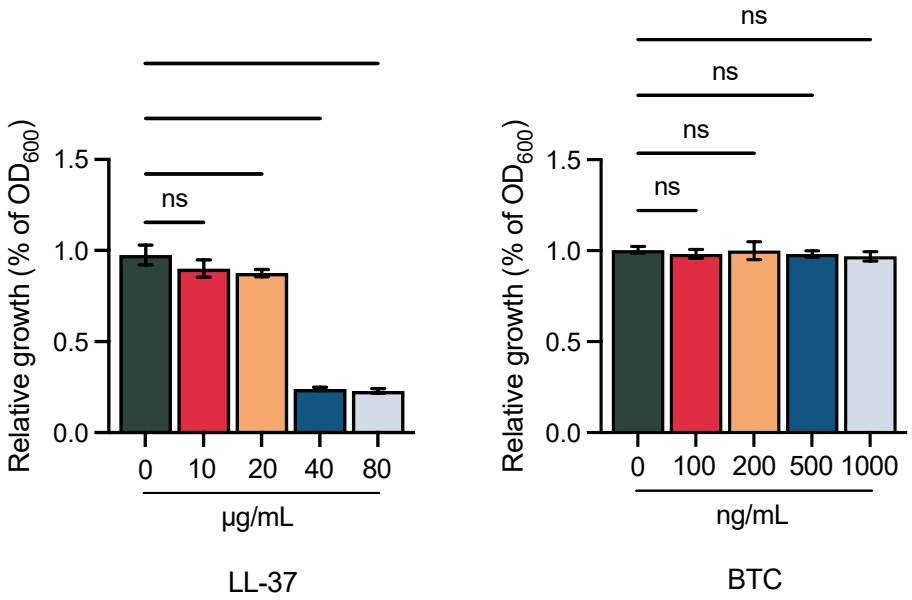
Choi SY et al. *Biomed Res Int*. 2018.

EGF relieved *S. aureus*-induced inflammation and AD-like skin lesions.

Our results:



How about BTC?

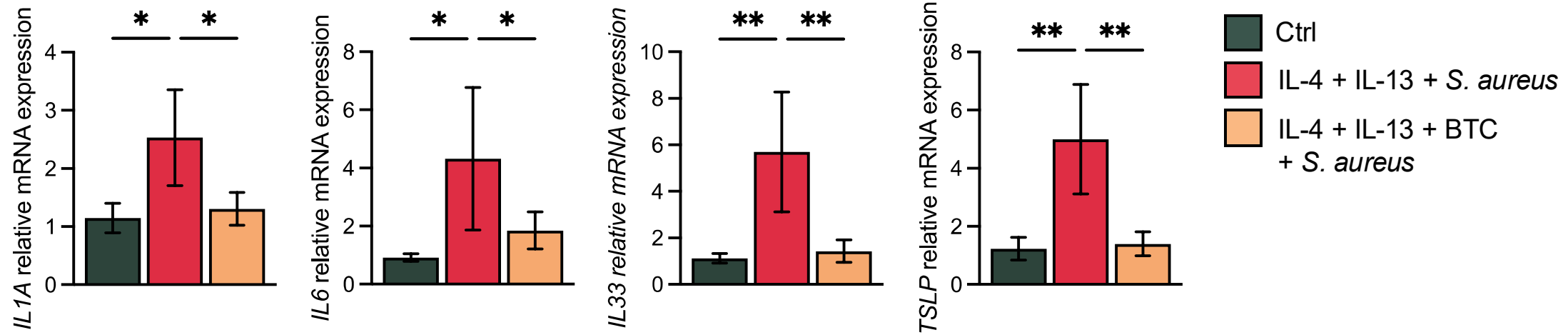


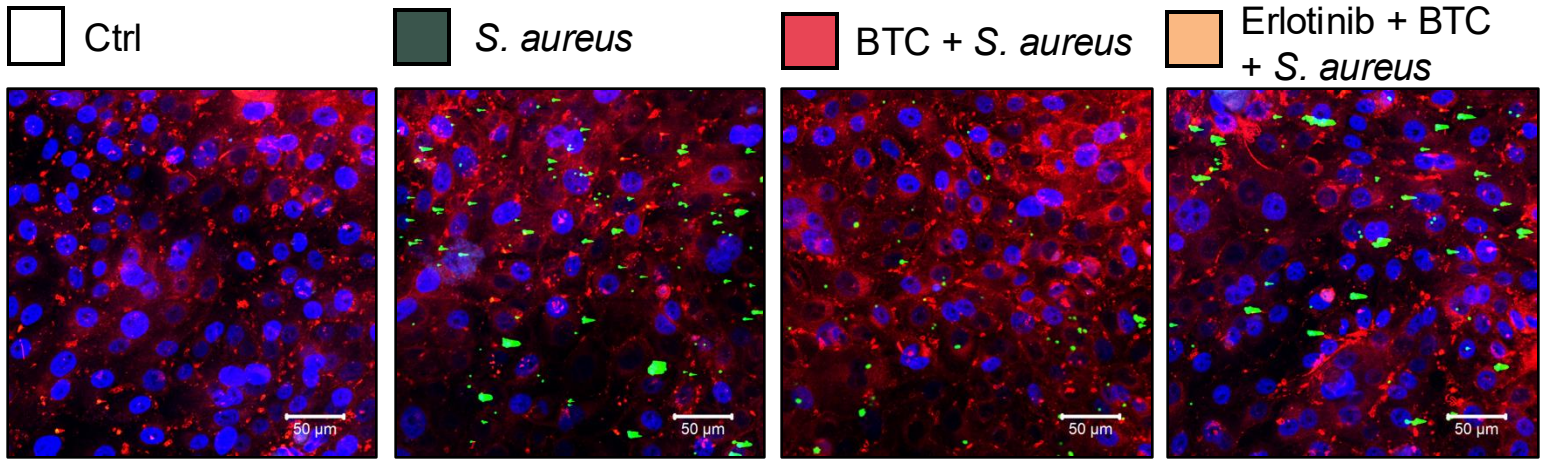
LL-37 is the only cathelicidin-derived antimicrobial peptide found in humans

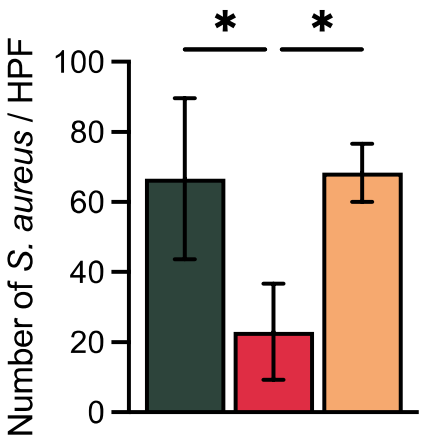
BTC does not directly kill *S. aureus*.

BTC has the potent suppressive effect on *S. aureus*-induced inflammation and invasion

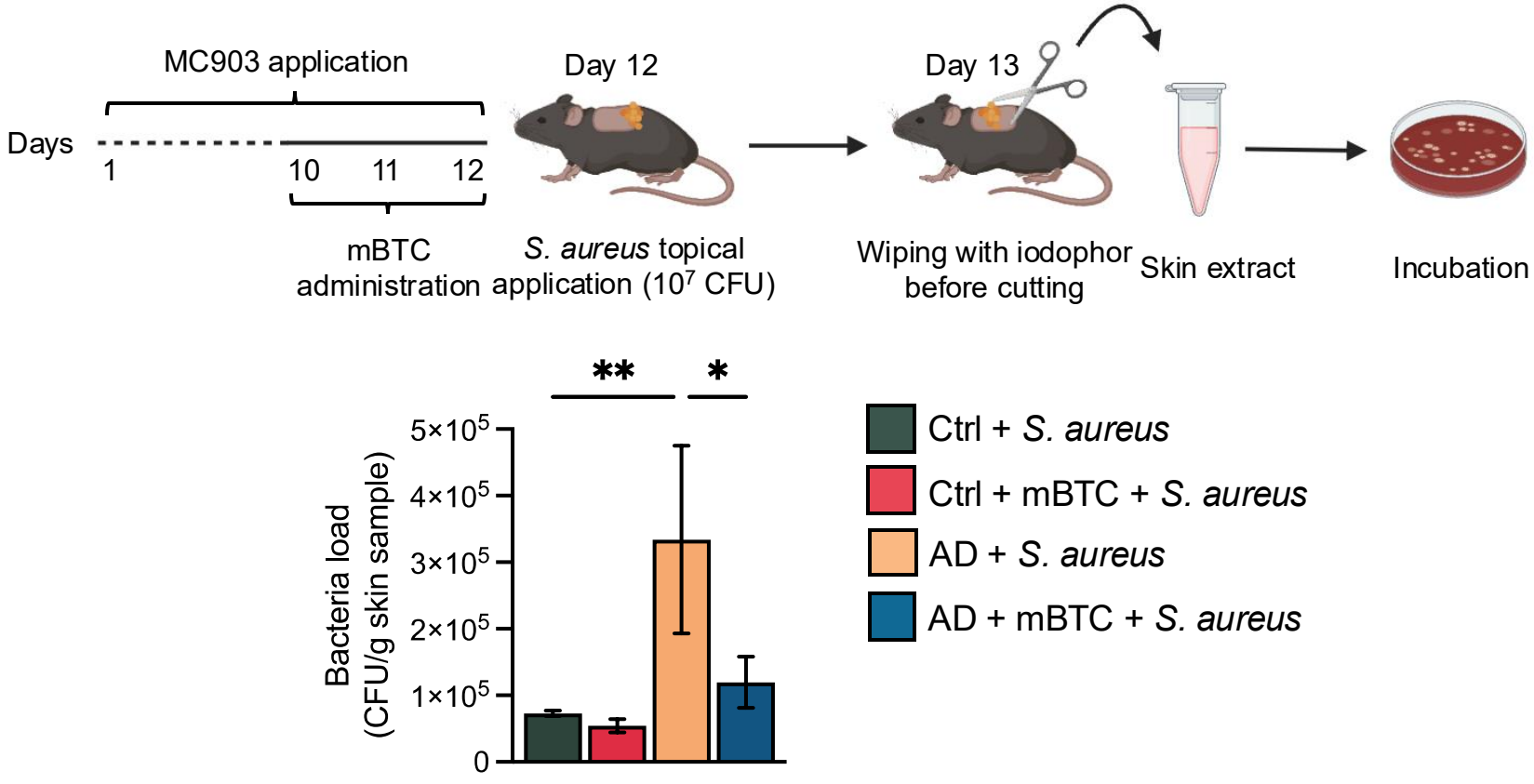
- In human keratinocytes







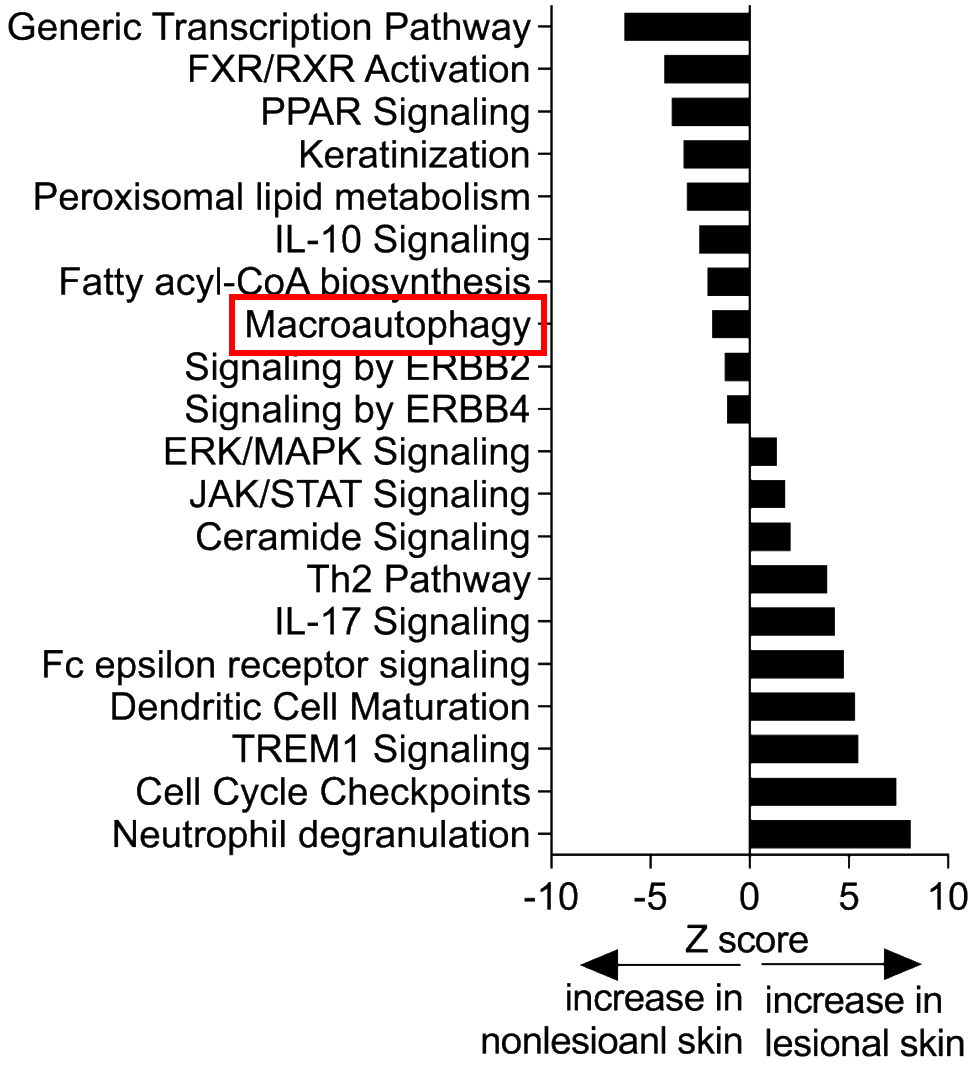
BTC has the potent suppressive effect on *S. aureus*-induced inflammation and invasion



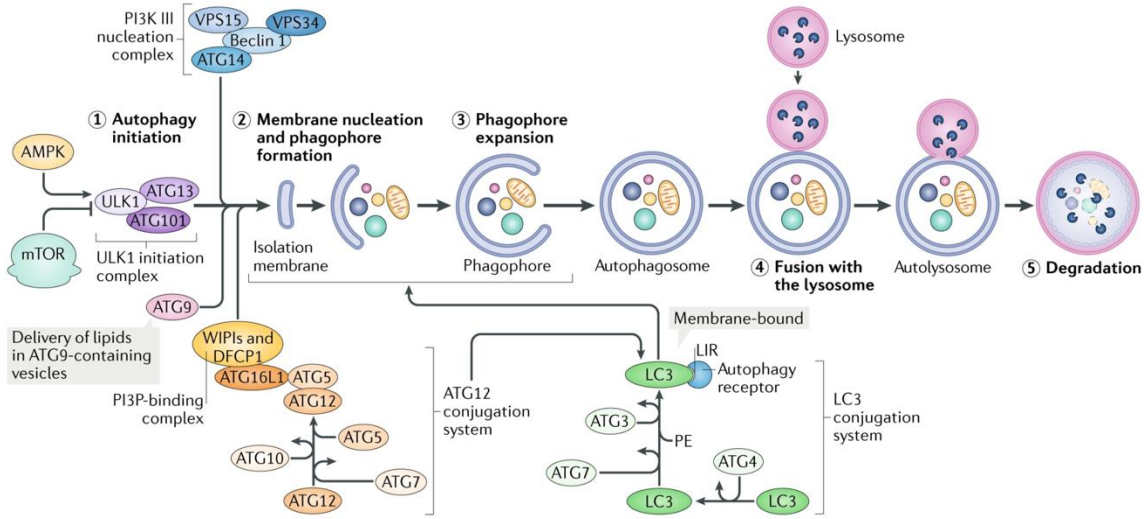
Summary 2: BTC does not show antimicrobial effect on *S. aureus*, but it may play a role in reducing *S. aureus*-induced inflammation and invasion in AD.

Autophagy pathway is downregulated in AD lesional skin

Ingenuity Pathways Analysis (IPA) of differentially expressed genes between lesional and nonlesional skin in AD patients

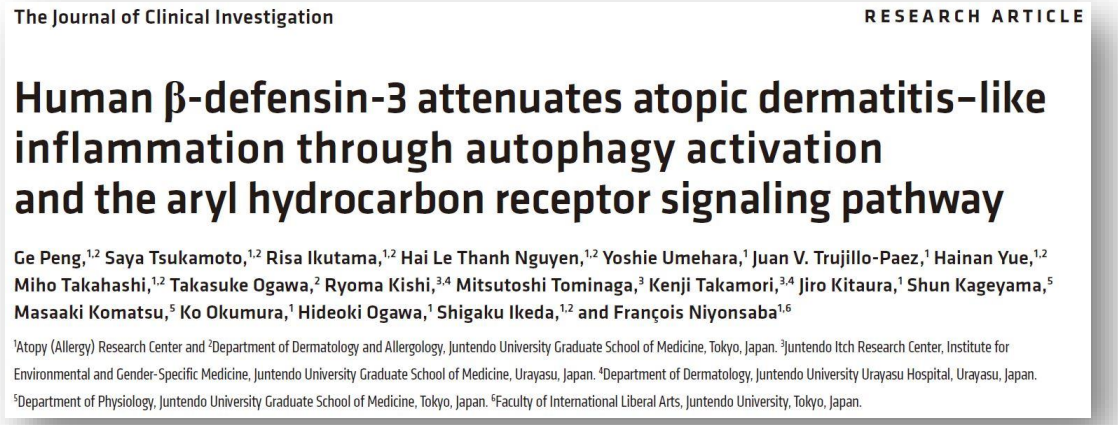


Autophagy in AD



Hansen M et al. *Nat Rev Mol Cell Biol*. 2018.

- Autophagy is a core molecular pathway for the preservation of cellular and organismal homeostasis.



The Journal of Clinical Investigation RESEARCH ARTICLE

Human β-defensin-3 attenuates atopic dermatitis–like inflammation through autophagy activation and the aryl hydrocarbon receptor signaling pathway

Ge Peng,[1,2] Saya Tsukamoto,[1,2] Risa Ikutama,[1,2] Hai Le Thanh Nguyen,[1,2] Yoshie Umehara,[1] Juan V. Trujillo-Paez,[1] Hainan Yue,[1,2] Miho Takahashi,[1,2] Takasuke Ogawa,[2] Ryoma Kishi,[3,4] Mitsutoshi Tominaga,[3] Kenji Takamori,[3,4] Jiro Kitaura,[1] Shun Kageyama,[5] Masaaki Komatsu,[5] Ko Okumura,[1] Hideoki Ogawa,[1] Shigaku Ikeda,[1,2] and François Niyonsaba[1,6]

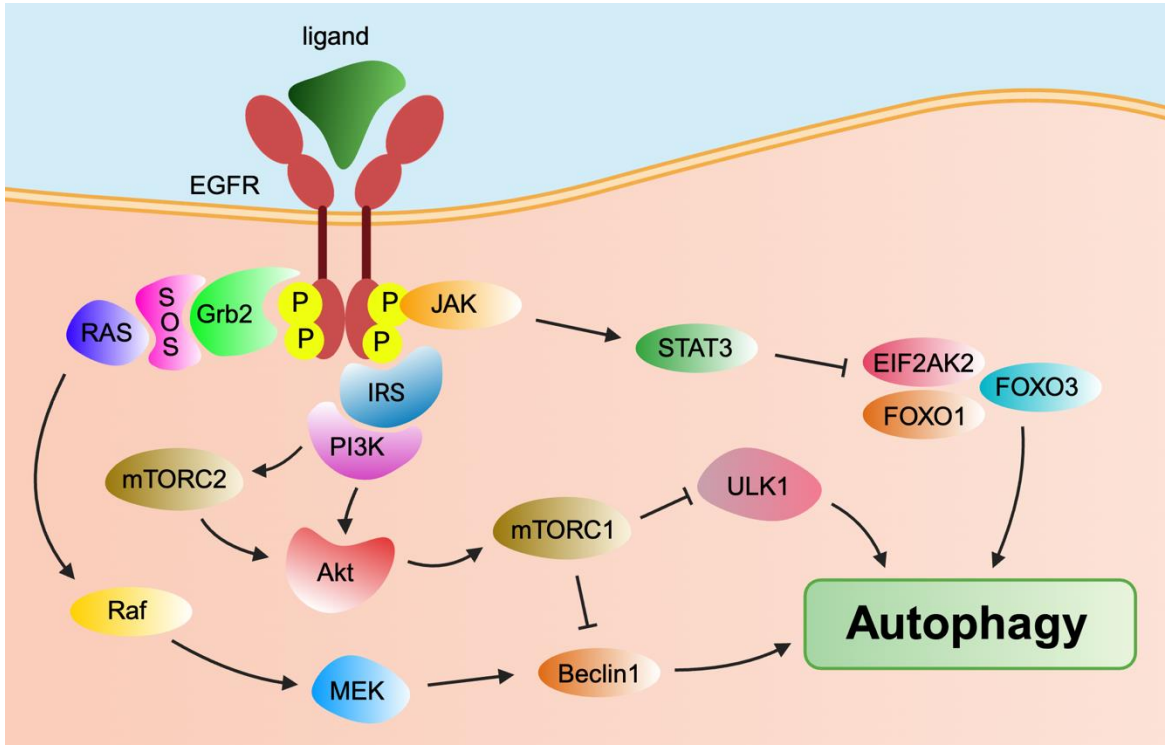
[1]Atopy (Allergy) Research Center and [2]Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo, Japan. [3]Juntendo Itch Research Center, Institute for Environmental and Gender-Specific Medicine, Juntendo University Graduate School of Medicine, Urayasu, Japan. [4]Department of Dermatology, Juntendo University Urayasu Hospital, Urayasu, Japan. [5]Department of Physiology, Juntendo University Graduate School of Medicine, Tokyo, Japan. [6]Faculty of International Liberal Arts, Juntendo University, Tokyo, Japan.

Peng G et al. *J Clin Invest*. 2022.

- Dysfunctional autophagy plays a crucial role in causing epidermal barrier defects that sustain chronic inflammation in AD. hBD-3-induced autophagy attenuates skin inflammation and enhances the TJ barrier in AD.

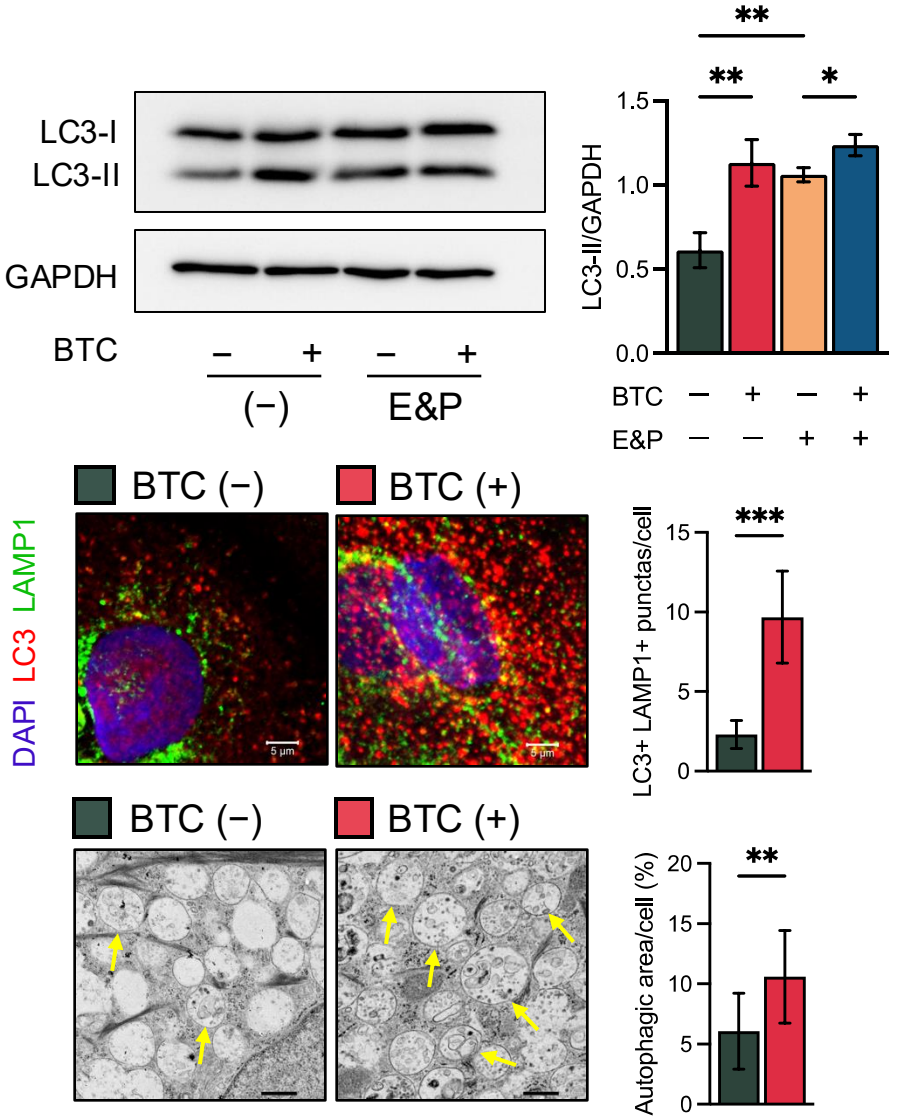
BTC induces autophagy activation in human keratinocytes

- The dual role of EGFR signaling in the regulation of autophagy



Modified from Wang J, et al. *Mol Cell Biochem*. 2022

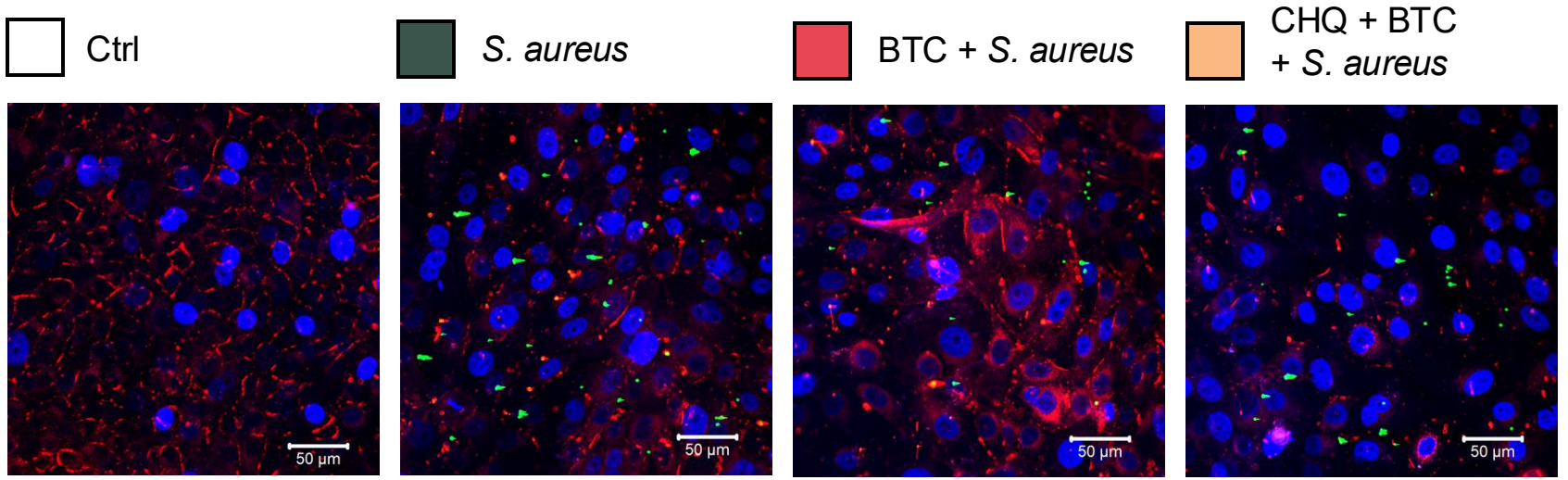
The potential of BTC to induce autophagy activation in keratinocytes is needed to explored

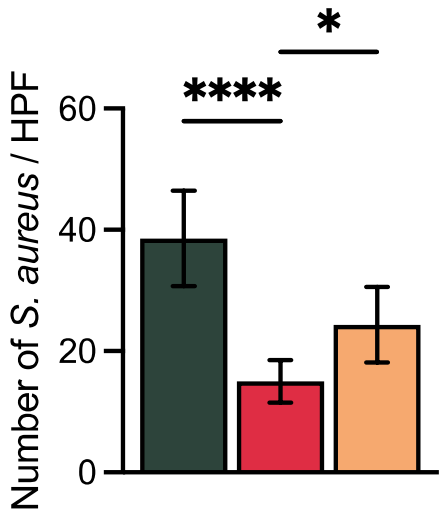


Summary 3: BTC induces autophagy in keratinocytes

Autophagy contributes to BTC-mediated suppressive effect on *S. aureus* invasion

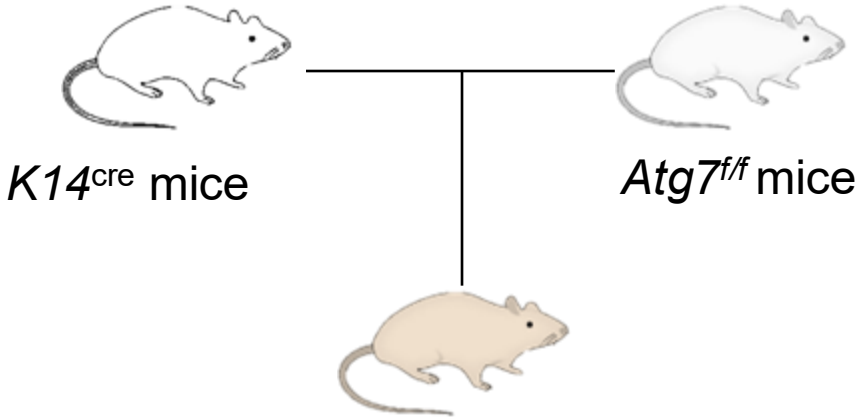
- In human keratinocytes

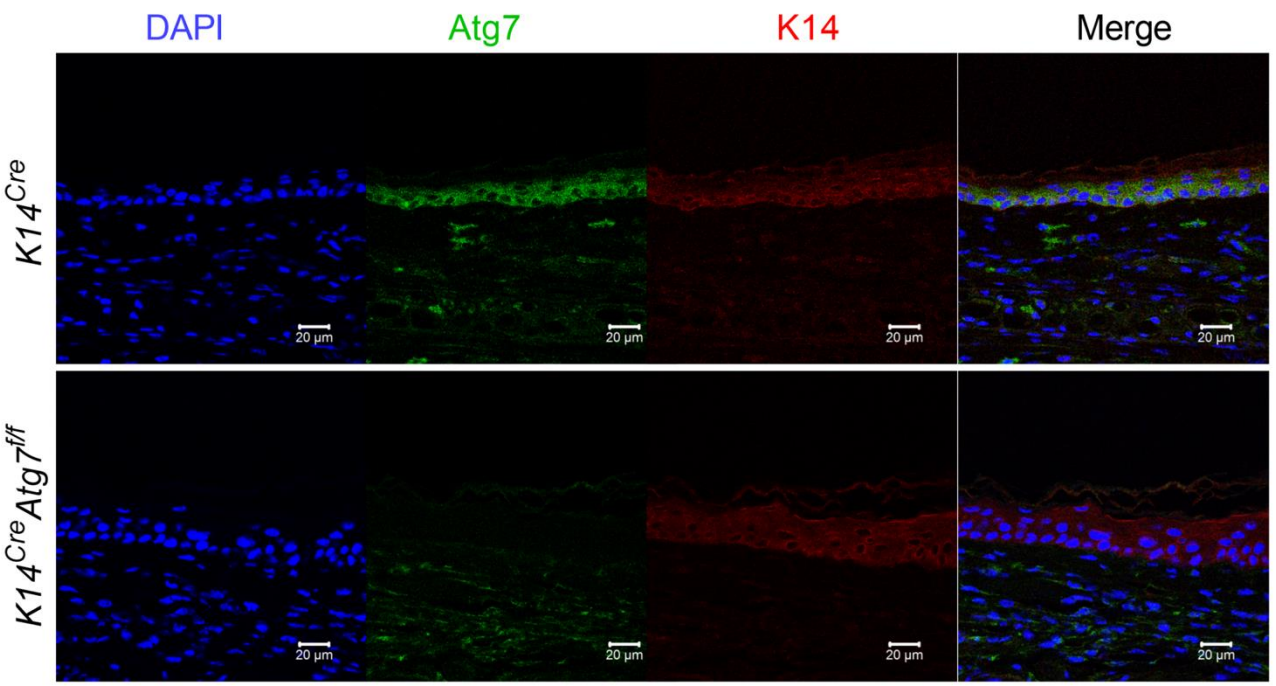


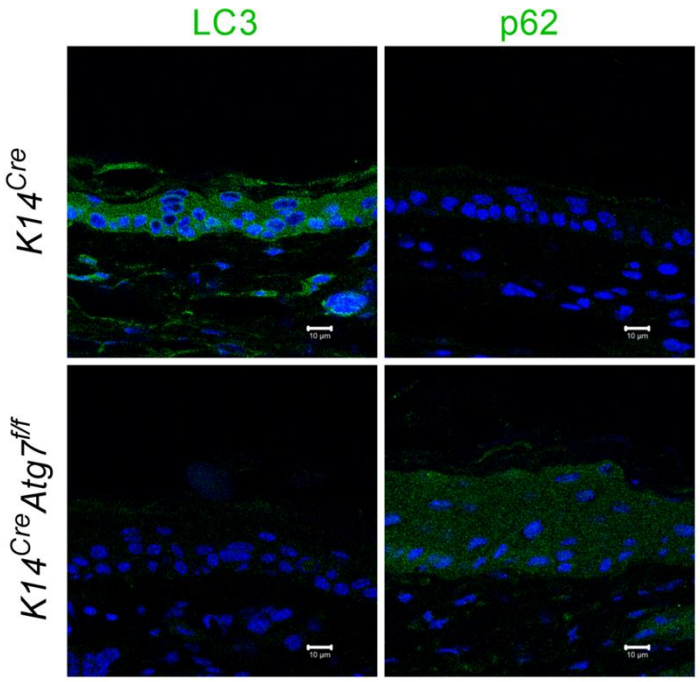


CHQ: chloroquine, an autophagy inhibitor that works by blocking the fusion of autophagosomes with lysosomes.

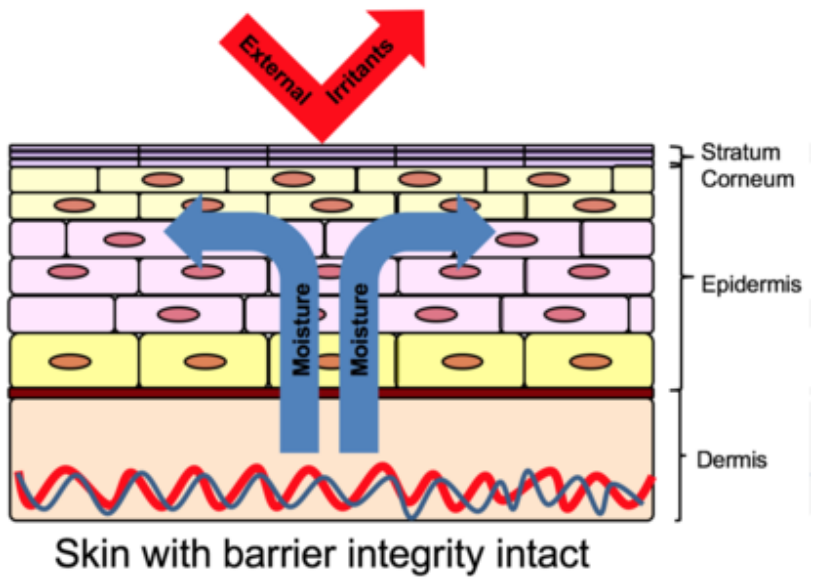
Generation of skin-specific autophagy deficient mice



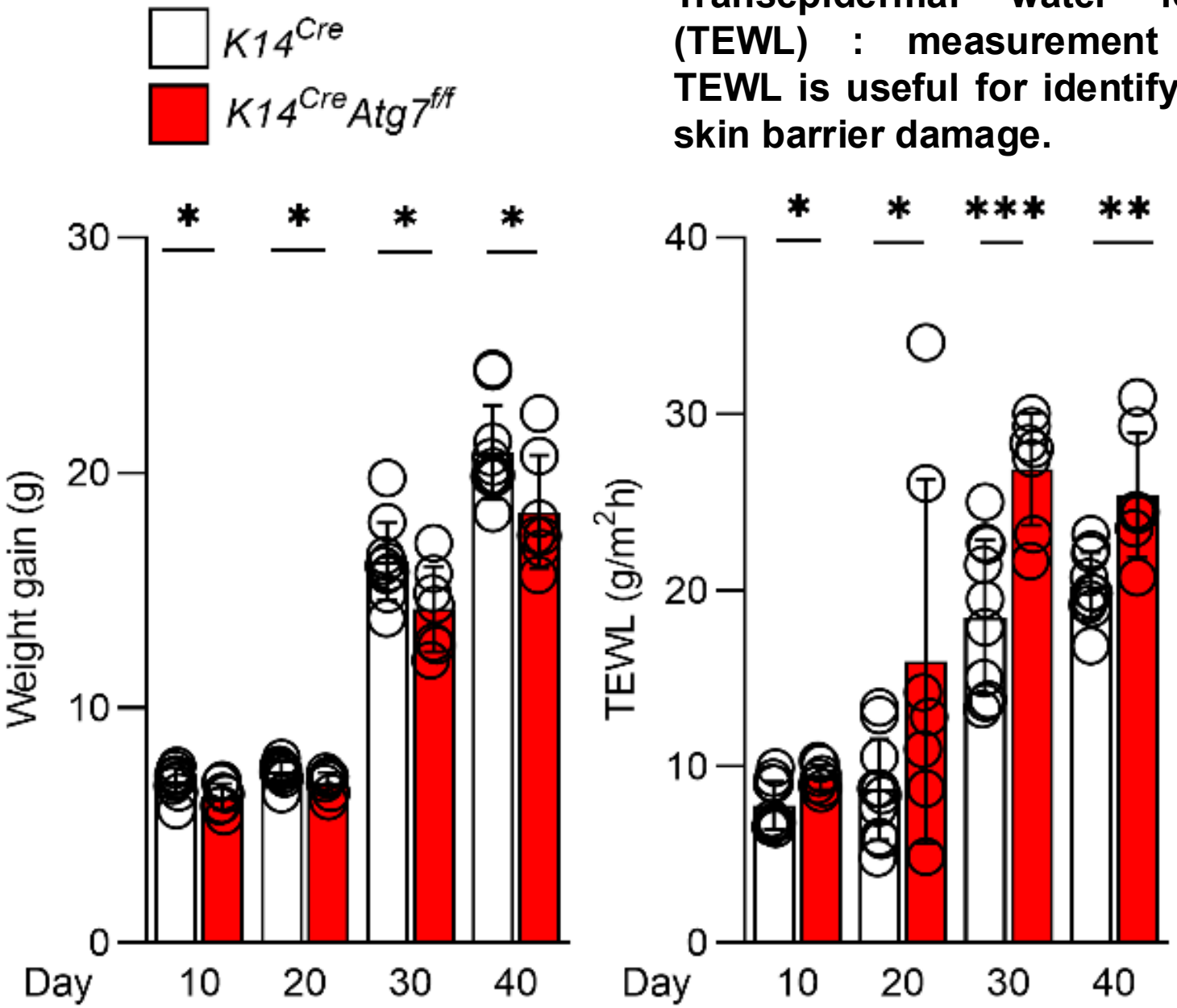




Alteration of body weight and TEWL in K14creAtg7F/F mice



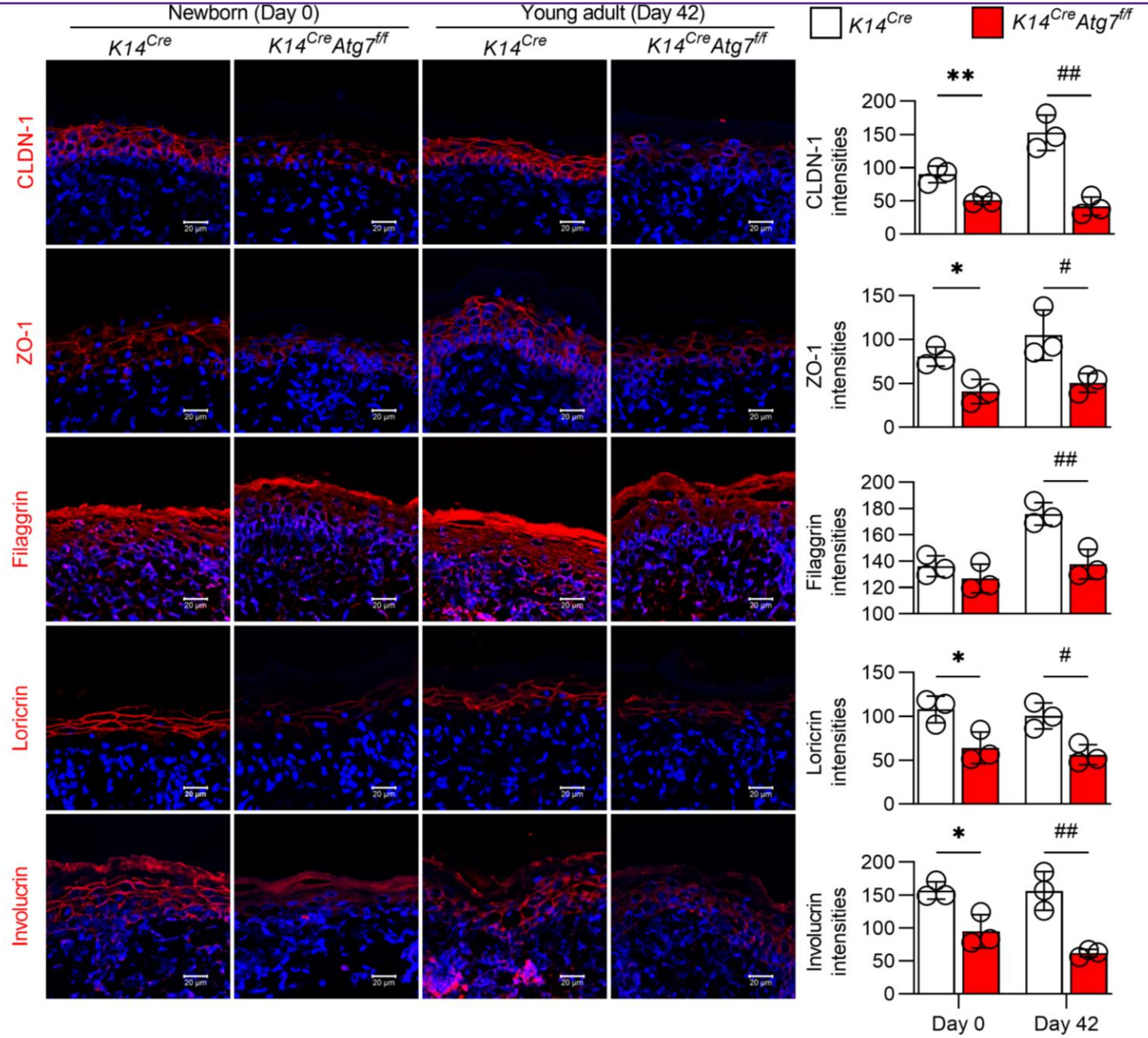
Transepidermal water loss (TEWL) : measurement of TEWL is useful for identifying skin barrier damage.



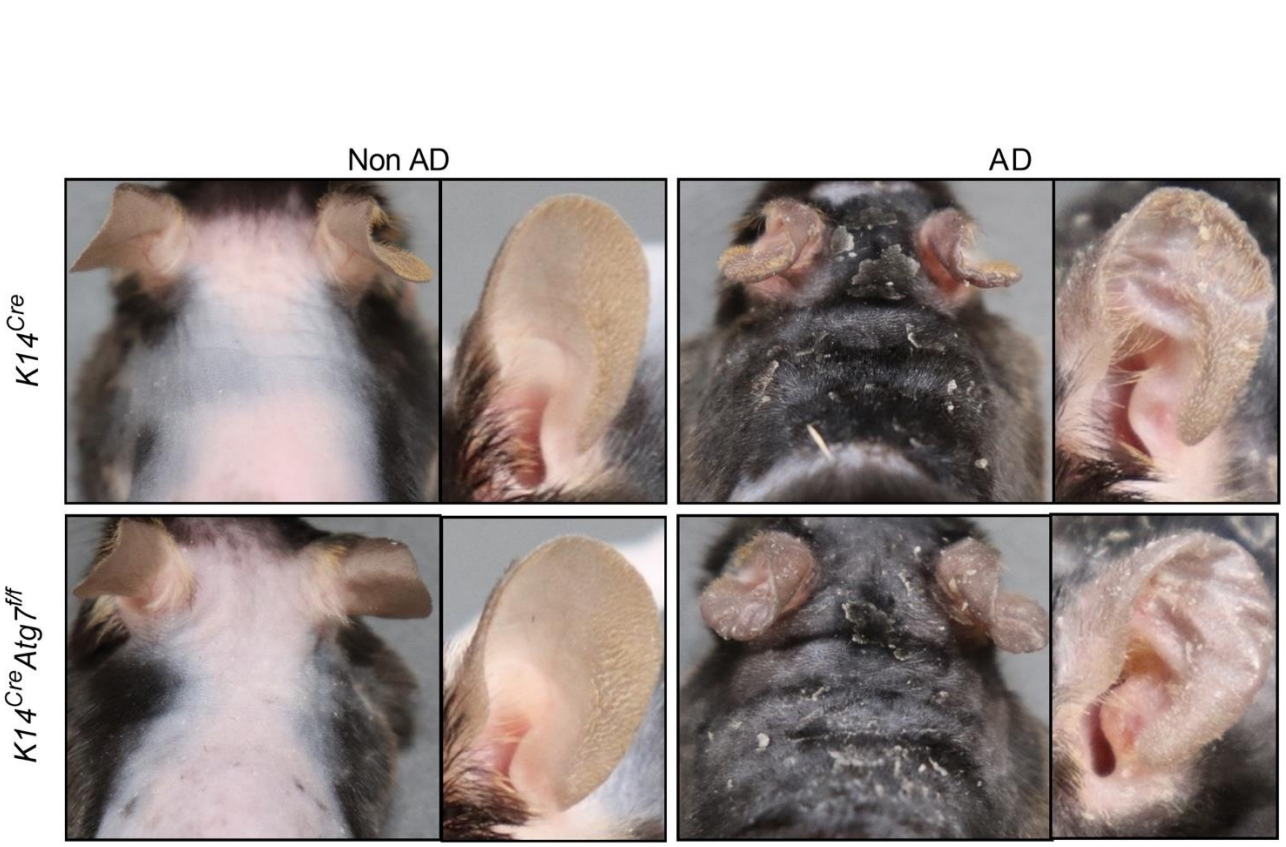
Autophagy deficiency downregulated skin barrier-related proteins in mice

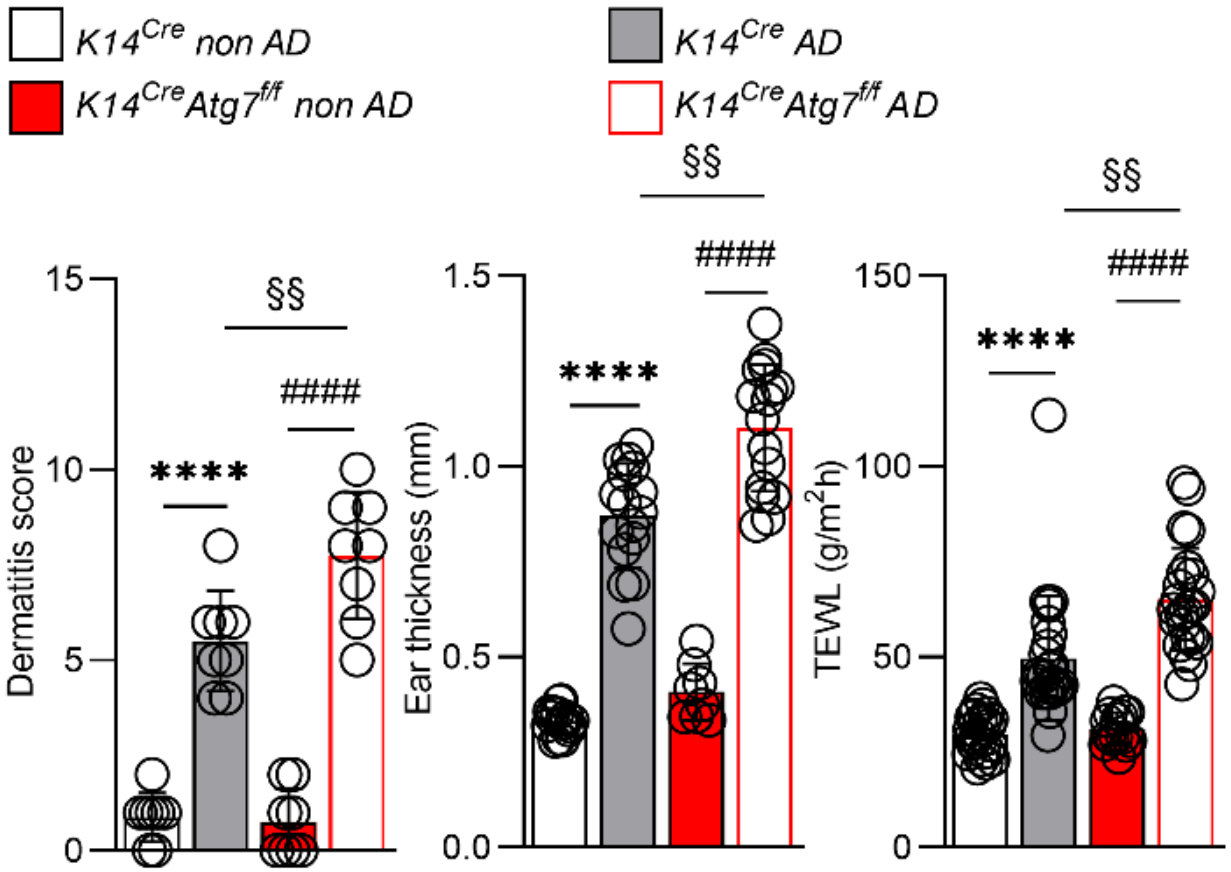
Skin barrier related proteins:

- Claudin-1 (CLDN-1)
- *Zonula occludens-1* (ZO-1)
- Filaggrin
- Loricrin
- Involucrin

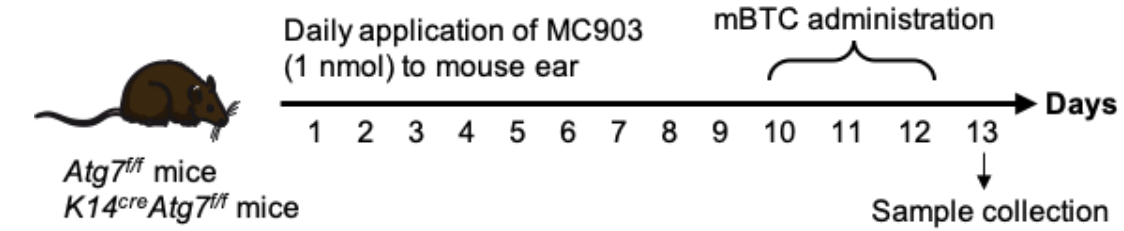


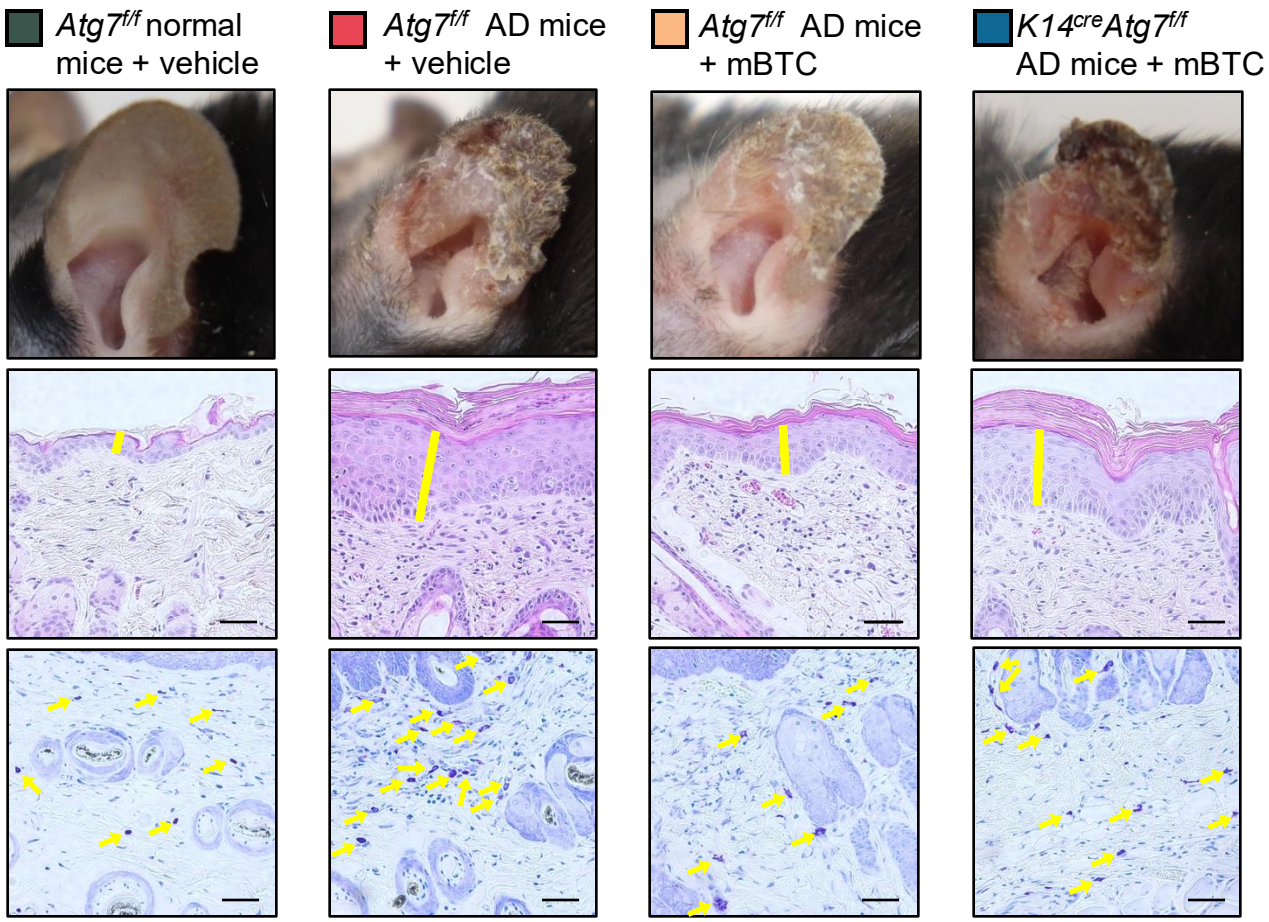
Autophagy deficiency exacerbated inflammatory symptoms in AD mice

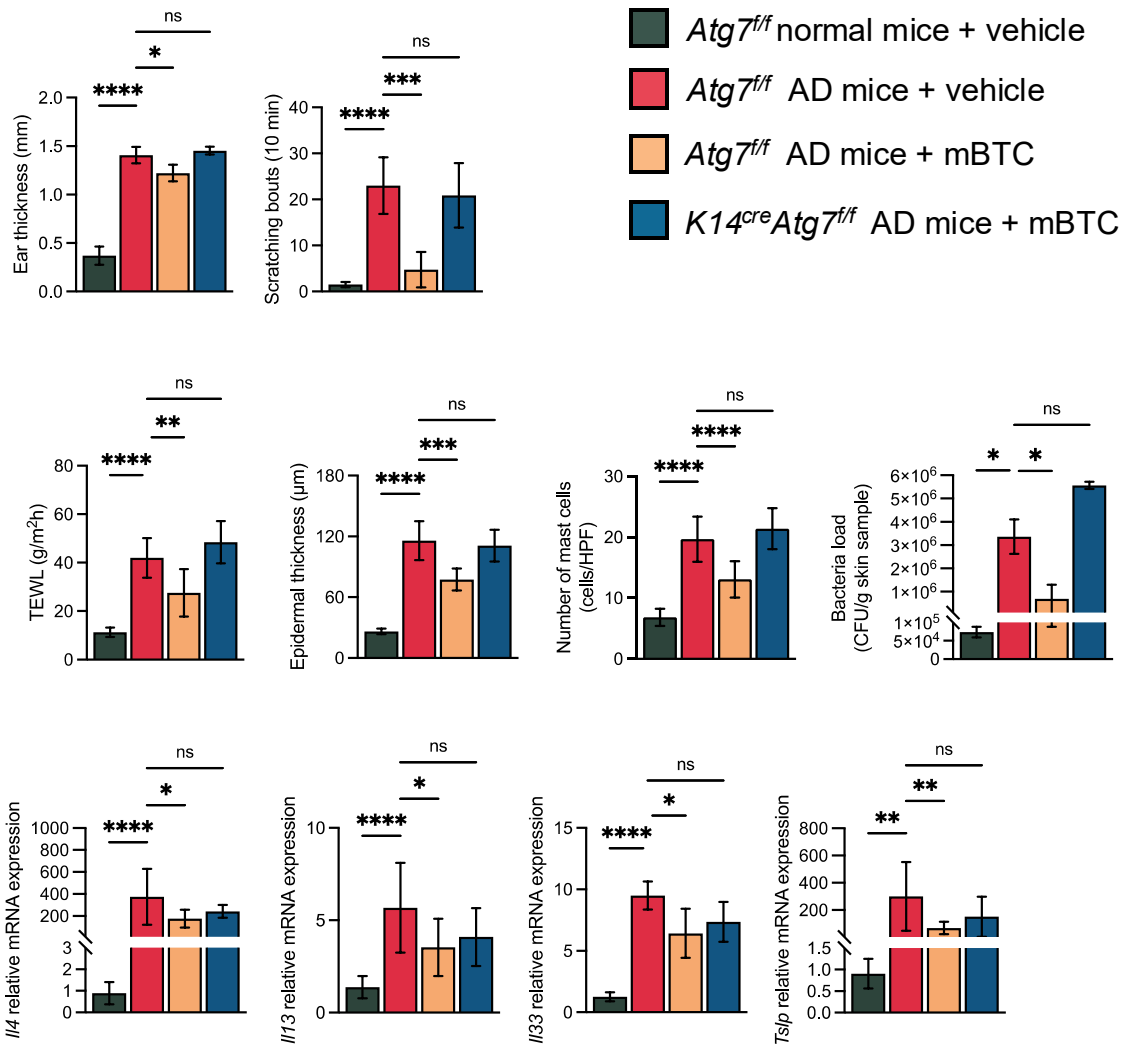




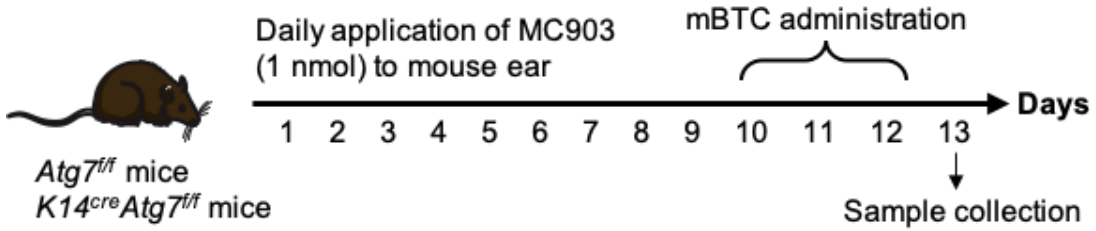
Autophagy contributes to BTC-mediated improvement in AD mice

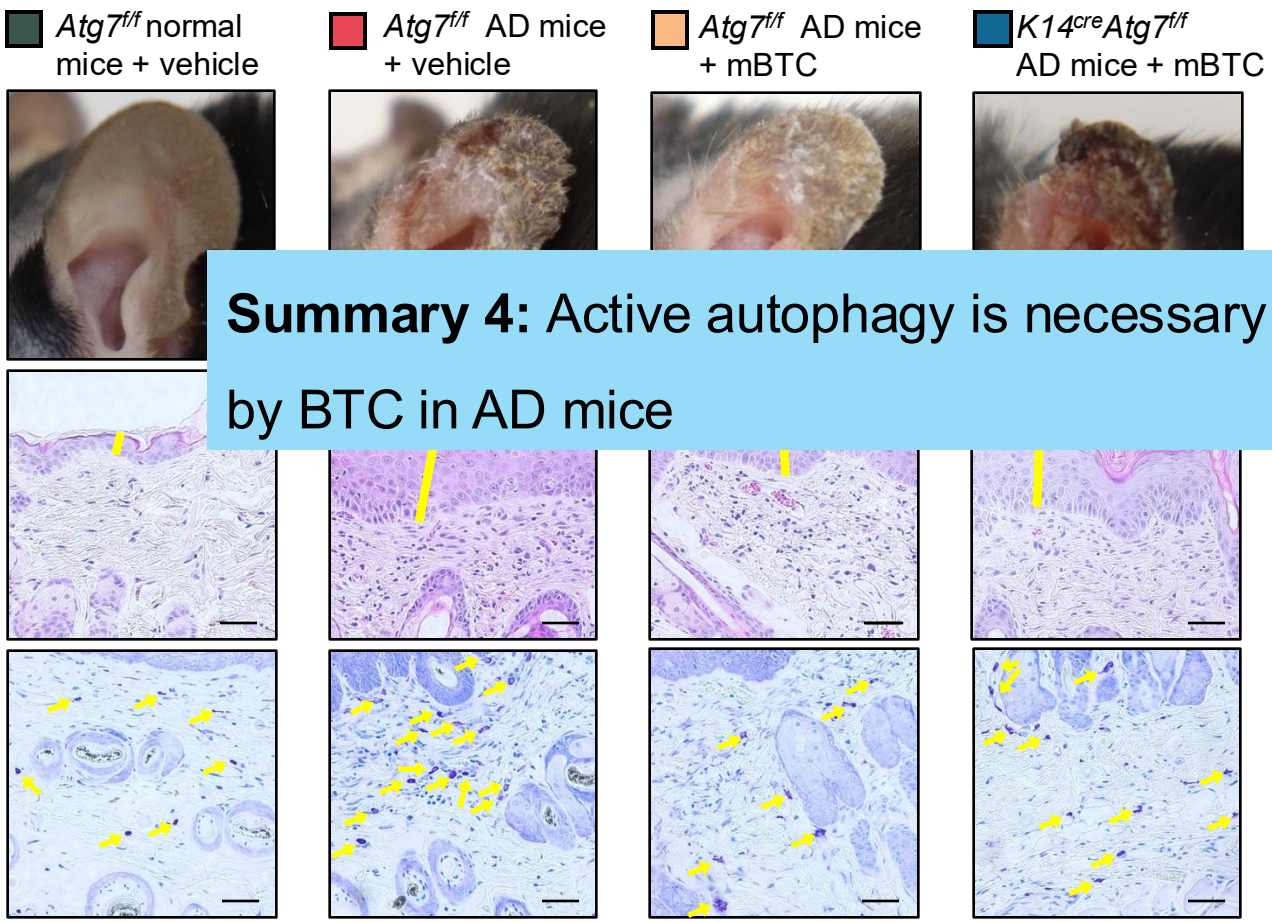


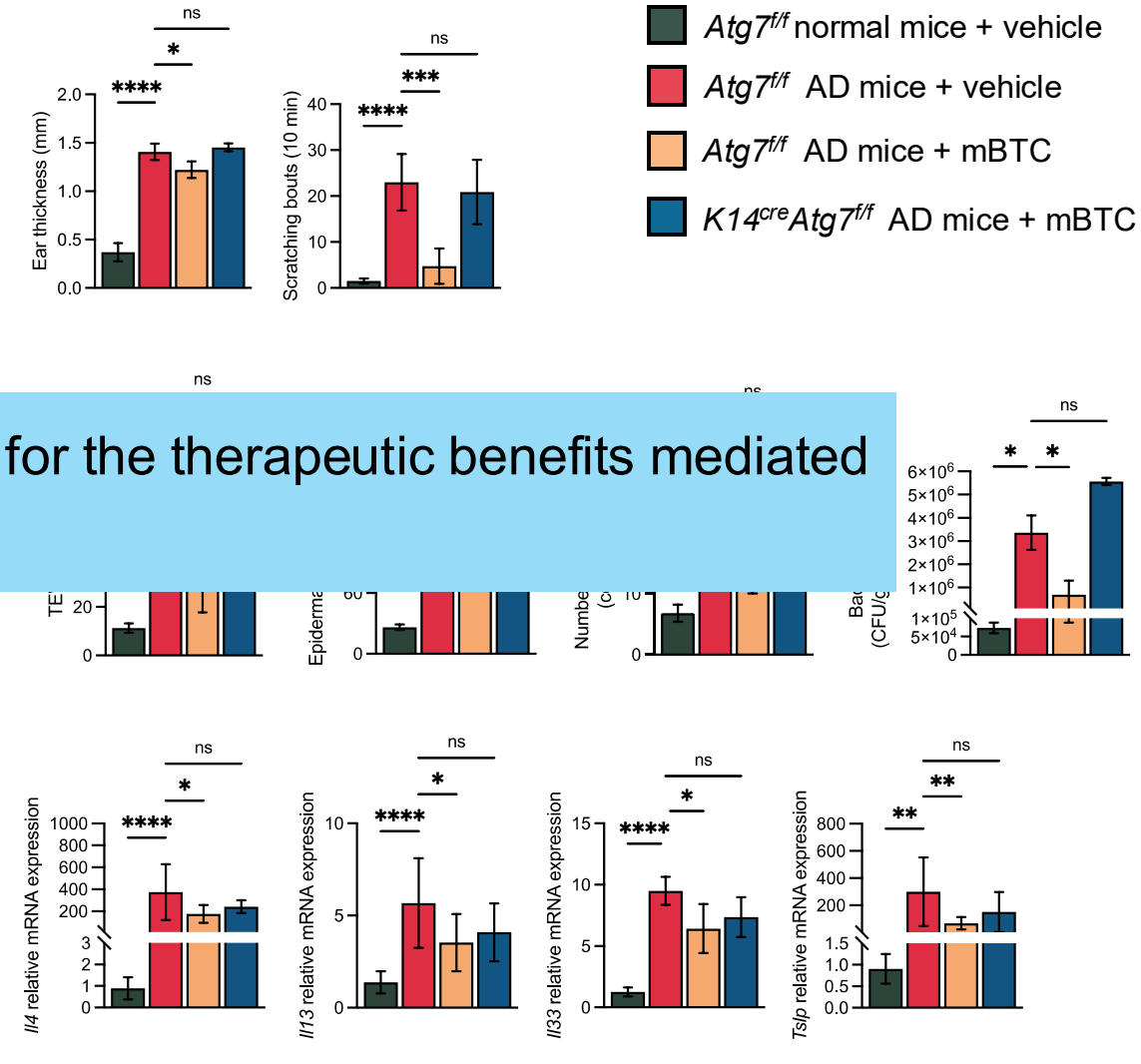




Autophagy contributes to BTC-mediated improvement in AD mice







Summary 4: Active autophagy is necessary for the therapeutic benefits mediated by BTC in AD mice

Conclusion

- BTC alleviates MC903-induced AD-like symptoms in a murine model.
- BTC has the potent suppressive effects on *S. aureus*-induced inflammation and *S. aureus* invasion.
- BTC induces autophagy activation in human primary keratinocytes.
- Autophagy contributes to BTC-mediated alleviation in AD mice.

Targeting autophagy is a promising option for AD treatment, and BTC may have the potential to be a novel therapeutic approach.

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Thanks for your attention!